ON INFLAMMATION.

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Sir James Paget's Bart.
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ON INFLAMMATION.

CHAPTER I.

Inflammation, the pivot, according to the late Professor Bennett, upon which medical philosophy has revolved in all ages, is a comprehensive term which embraces a number of changes in the elements which compose animal tissues. The nature and sequence of these changes are ill understood, and are consequently subjects of unending controversy. And when it is considered that the normal structure of the tissues in which the changes take place, is just as much subject of controversy as the inflammatory changes which take place in them, we cannot wonder that the nature of inflammation continues to divide successive generations and the different contemporary schools of pathology. In beginning the study of inflammation, it becomes therefore absolutely necessary to consider first how much it is possible to know of the healthy tissues.

Investigations into the nature of connective tissue having led me to different conclusions from those which have been hitherto taught, I applied them to an experimental study of the nature of inflammatory change, and I believe I have found in them a key to the perplexing difficulties which meet any one who endeavours to reconcile the conflicting observations of the schools of Stricker, Colnheim, and other contemporary writers. In this number, I shall therefore, as a fit introduction to the subject, endeavour to explain what I believe to be the general plan on which all the connective tissues are formed. As the studies to which I have referred have been largely made on the cornea, and as most of the observations by myself and others to which I shall afterwards refer, have been made on the inflamed cornea, it is convenient that I begin by a study of that structure. I will then

show that it can be considered as typical of the other forms of the tissue.

The substance proper of the cornea may, like other forms of fibrillary tissue, but not so readily as some of them, be resolved into exceedingly fine fibrillæ, whose diameter it is impossible to measure with accuracy.

In a cornea which has been sealed on an object-glass in aqueous humour, and in which a few incisions have been previously made in different directions, there may, in some instances, after twenty-four to forty-eight hours, be observed, lying free between the edges of the incisions, long, even, straight-contoured bands of various length. Their breadth in the frog approaches the diameter of a human red blood-corpuscle, and they are all of equal breadth and thickness.

In the edges of the incisions, similar bands may be seen lying parallel to each other, and occasionally they may be seen in uncut portions of the cornea. A cornea similarly treated, and sealed up in a mixture of gold solution[1] and acetic acid, occasionally shows the same appearances.

Considering the fibrilla as unity, I shall for convenience apply the term primary bundle to these bands.

Fig. 1 represents two of a group which were examined in aqueous humour.

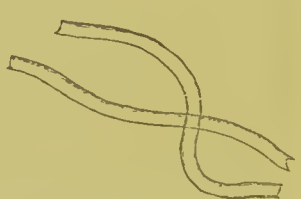

Fig. 1.—Primary bundles from a frog's cornea in aqueous humour. —Hartnack, Obj. 8, Oc. 3.

In sections of the cornea treated in gold, and in teased preparations variously obtained, broader bands of fibrillary substance can be seen more or less perfectly isolated. These correspond to the so-called "bundles" of fibrillary tissue, the existence of the definite element which I have designated as a "primary bundle" not having been recognised. The "bundle" of authors I shall distinguish as a *secondary* bundle. It is composed of a number of primary bundles applied parallel to each other.

The anterior surface of a cornea carefully examined in aqueous humour, may be frequently seen to be intersected by clefts. They are recognisable by the distinct double contour of their borders, and their detection is facilitated by examining a frog's cornea in blood serum which contains a considerable number of blood-corpuscles. The red corpuscles, in virtue of some attraction or current, find

[1] The gold solution here and afterwards referred to is prepared by dissolving 1 gramme (15 grains) of chloride of gold in 200 cent. cub. (7 ounces) of distilled water.

their way into the clefts, and, being drawn into the narrowing channel, they are seen at some parts of it as long narrow bodies.

On careful examination, it can be sometimes seen that even at the narrowest parts the superficial epithelium does not bridge the cleft, but dips into it over each edge. The clefts are wider nearer the limbus, and run obliquely into the substance of the cornea, occasionally diverging as they approach its centre. When once seen, they need never afterwards be confounded with the nerves of the cornea. They are more easily recognised in inflamed preparations.

These clefts indicate a further arrangement of the fibrillary substance into tracts or compartments, which, if the phraseology of "bundles" is to be adhered to, might be designated tertiary bundles.

Horizontal layers of cornea substance, thicker than the lamellæ seen under the microscope in a vertical section, may be detached from a cornea which has been for some days in weak acetic acid. Those, I believe, have a relation to layers which actually exist, because in the same animals the relative number of lamellæ so obtainable is approximatively the same, and because, as I shall subsequently show, they correspond to continuous layers of flat cells in the substance of the cornea, which, we are justified by all analogy in assuming, cover free surfaces.

When a cornea is placed 15 to 25 minutes in solution of chloride of gold, and is then allowed to remain exposed to a bright light for several days in distilled water, made faintly sour by adding a few drops of acetic acid, there will usually be seen interspersed through its substance large nuclei, surrounded by a dark purple granular deposit, which is continued in straight projections of varying breadth in all directions, their anastomosis forming a network.

This appearance is believed by many histologists[1] to coincide with a system of branched anastomosing cells, the dark purple deposit representing the cell and its processes. The constant presence of a nucleus in the centre of the mass undoubtedly renders the interpretation a plausible one. But it is nothing better than a hypothesis. If any one chooses to say that the presence of a nucleus in the central points of a network which varies exceedingly even in animals of the same species, is no proof that the network stands in the relation of a cell to the nucleus, the objection is unanswerable. All that the gold preparations have shown is, that the constancy with which the metallic deposit has taken place in the same general form indicates a structural peculiarity

[1] See, for example, Rollett, Stricker's Handbook p. 1101 (German edition).

of the cornea, and the uniform presence of a nucleus in the central points indicates that there is a cell there.

To ascertain definitely the nature of the cell of which the nucleus is so easily made visible, it is necessary to have recourse to other methods.

By examining the cornea of a frog or a transverse section of a larger cornea made with a sharp razor some hours after death, with an immersion lens, it is possible to see the same large nucleus which is visible in gold preparations, and immediately surrounding it a mass of branched protoplasm which by its appearance and contours differs from the metallic gold deposit. Fig. 2 shows such a cell and processes from the ox cornea.

Fig. 2.—Stellate cell from ox cornea. Fresh. Mag. 800 diameters.

In a similar section sealed in aqueons humour the cell and its processes become still more sharply defined. Fig. 3 shows a stellate cell from a sheep's cornea after being sealed twenty hours.

Fig. 3.—Stellate cell from sheep's cornea, twenty hours sealed in aq. hum.—Hartnack, Obj. 8, Oc. 3.

If a cornea has been subjected before the death of the animal to irritation sufficient to produce distension by serous effusion, and the excised cornea is placed for twenty-four hours in a solution of one part osmic acid in 200 water, transverse sections made without further preparation, and examined in glycerine, frequently show the stellate cells and their anastomosing processes. If the section is stained by logwood, the nucleus is also visible. It is then seen

Fig. 4.—Stellate cells with anastomosing processes, from a rabbit's cornea. Osmic acid preparation.—Hartnack, Obj. 8, Oc. 3.

that some of the anastomosing processes are of great length. Fig. 4 shows a long anastomosing process connecting two cells in an

osmic acid preparation of a rabbit's cornea. The other processes are not shown. The length in the figure is the apparent length seen under the microscope as nearly as could be judged by the eye.

To demonstrate the branched cells of the cornea, I have lately practised a more satisfactory method than any other previously known to me, the object aimed at being to inject the interfascicular spaces by gold solution from the carotid. When sufficient pressure is maintained for a few minutes after the eyeball has become tense, the solution penetrates the cornea from the conjunctival vessels. I have then usually placed the excised eyeball entire in gold solution for about an hour, and at intervals made small incisions at different parts of the corneal surface, and then placed the eye, still entire, for twenty-four hours in faintly acid water. When the operation has been successful, such a cornea presents under the microscope an appearance that will strike a histologist who sees it for the first time with astonishment. Long, straight, anastomosing fibres cross the field transversely and obliquely in all directions. These fibres have all the objective characters by which we distinguish elastic fibres, and the stellate cell-protoplasma, shrunk by the solution, is seen adherent to the central points of the network. Such preparations as I have hitherto obtained were examined in glycerine, in which unfortunately after a very short time the fibres cease to be visible.

In one of my preparations I cut the cornea in small fragments with a knife, and then succeeded in obtaining isolated cells with parts of the processes of various lengths still adherent.

My best preparations of this series were from the cornea of young rabbits.

In studying the nuclei of the different corneal cells, it is to be borne in mind that the stellate nucleus can always be recognised by its size. It is larger than the nucleus of any other cell which is found in the cornea, and is the only cellular element that has been usually seen. The so-called cornea-corpuscle of authors is, as can be seen by their figures, nothing but this nucleus surrounded by amorphous deposit in the interfascicular spaces.

In a frog's cornea, sealed in a mixture of gold solution and acetic acid, very delicate spindle elements are sometimes visible, but they are seen much more satisfactorily in a cornea injected from the carotid by gold solution. They can be readily recognised in the same field as the stellate cells, and in a good preparation their number is very striking. They lie in parallel chains, distant from each other by the breadth of a primary bundle. Two can fre-

quently be seen lying side by side in the same interfascicular space. The small size of the nucleus—smaller than any nucleus that has been hitherto recognised—and the disposition of the scant protoplasma in spindle shape, distinguish them from the stellate cells. In a frog's cornea injected by gold, it sometimes happens that the spindle cells processes and nuclei are visible, whilst nothing of the stellate cells but the nuclei is visible. Larger spindle nuclei and cells are seen in the tracts of the nerves, and between the larger cornea bundles. The above methods are alone reliable for demonstration of the spindle cells. They are essentially distinct from the stellate cells, with which they can never be confounded when they have been once seen.

Fig. 5.—From cornea of a frog injected by gold solution from the aorta. *Sp*, spindle cell and nucleus. *St*, nucleus of a stellate cell.—Hartnack, Obj 8, Oc. 3.

The size and relative position of the spindle cells towards each other and to the stellate nucleus is shown in Fig. 5. The recognition of spindle cells in the cornea, apart from its interest, looked at from a purely histological point of view, is of great importance, as we shall afterwards see in stndying the inflamed cornea. In inflamed tissue they are shown conspicuously by nearly every method of investigation usually employed, and they have been confounded with white blood corpuscles on the one hand, and with products of "proliferation" on the other.

Fig. 6.—Spindle elements in muscular fibre of frog. Gold and acetic acid mixture.—Hartnack. Obj. 10 (immersion). Oc. 3.

These spindle cells of the cornea correspond in size and position relatively to each other, and to the primary bundles with similar spindle elements in muscular fibres, which I described in a previous paper in this Journal (September 1874), as will be evident from a comparison of Fig. 5 with Fig. 6.

In the previous paper on muscle, being then ignorant of the existence of these fine spindle elements in connective tissue, I termed them, in my description of Fig. 6, "longitudinal fibres of elastic network," and in the text I spoke of them as "fine fibrillæ which present oval swellings at short intervals." I also stated that they communicate with a transverse network, which encloses

the primary bundles in its meshes. Subsequent investigations have shown me that I was mistaken in regard to this supposed communication between the two sets of fibres. The longitudinal elements seen in Fig. 6 are chains of minute spindle cells, which lie between the primary bundles of muscle, and are distinct both from the muscle fibrillæ and from the transverse network.[1]

When the temperature produced by the solution of caustic potash in an equal weight of distilled water falls to 107°–105° Fahr., a cornea, or part of a cornea, placed in the solution at that temperature becomes completely dissolved, with the exception of masses of cells, which can be seen isolated or in connexion with each other, when a part of the altered corneal mass is examined in a drop of the solution.

For a more complete account of these cells, the reader is referred to the paper in which I described them, in the *Proceedings of the Royal Society*, No. 155, 1874. In the Plate which accompanies that paper, figures are given, showing the relative

Fig. 7.—Flat cells from ox cornea by potash solution.—Hartnack, Obj. 8, Oc. 3.

position of the cells to each other. Fig. 7 shows the size and form of some of these cells.

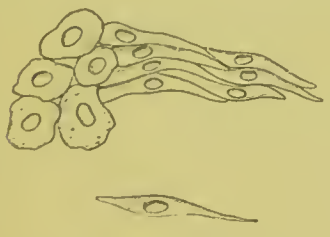

Fig. 8.—Isolated flat cells from obliquely cut sheep cornea two days soaked in aq. hum.—Hartnack, Obj. 8, Oc. 3.

In soaked aqueous humour preparations in which the cornea has been carefully cut obliquely, the same cells are seen isolated singly and in small masses, as is shown in Fig. 8. They are then seen as hyaline bodies, with a slightly projecting, faintly-tinged nucleus. In a preparation in which they are visible, they can usually be traced from the obliquely cut surfaces a certain distance into the structure. Sometimes, but much more rarely, a preparation is obtained, in which their position relatively to the bundles is distinct. Such a preparation is represented in Fig. 9. It is then seen that the long narrow cells are applied to the surfaces

[1] I take this opportunity of correcting a misapprehension which I find some readers of my previous paper have fallen into, through my neglecting to state that the *acetic acid* which I used was not glacial acetic acid, but the weaker preparation known in England in commerce as "concentrated."

of the primary bundles, and that their edges are in contact after the manner of an epithelium, although, as will be seen from the figure, some of the cells become disintegrated, and disappear during the manipulation. In gold preparations, which have been prepared by placing the whole bulb for one to one and a half hour in the solution, removing the surface epithelium and making incisions in the cornea, and finally excising it and placing it in acidulated water, the polygonal and rounded cells can be seen to form layers in the substance of the cornea. Successful preparations of these cells by gold in the uninflamed cornea are very rarely obtained. In a very large number of corneæ treated in different ways by gold, I have only seen them three or four times. If the cornea has been irritated for a few hours, they are more frequently seen in gold preparations.

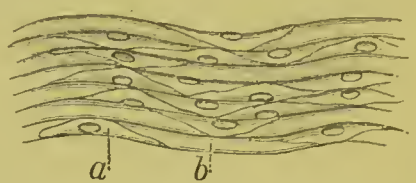

FIG. 9.—From frog's cornea sealed in aq. hum. Long narrow cells seen lying on the primary bundles. *a*, Cell. *b*, Part of primary bundle from which the cell has disappeared.—Hartnack, Obj. 8, Oc. 3.

It is to be noted that, although layers of the polygonal or rounded cells of the ordinary epithelial type can be seen of various sizes in the cornea, both in potash and aqueous humour preparations, patches can be isolated which are continuous with the long narrow cells that cover the primary bundles.

It was shown some years ago by Schweigger-Seidel, that there are cells in the cornea which show the dark lines of epithelium when treated by nitrate of silver. He was for an unusually long time in the minority of one, in which Carlyle says all truth begins. But the demonstration of the fact is not very difficult. Of all the animals on which I have operated, with a view to the demonstration of this epithelium, the cornea of the mouse is the best adapted, and gives most frequent success. The cornea is placed, unwashed, in solution of 1 part nitrate of silver in 200 or 400 water for one to three minutes, dipped for a second in salt solution of the same strength, and then exposed to sunlight in glycerine. The preparations which succeed best are those in which the ground substance is only slightly stained, being seen as faint brown islands scattered over a white field, instead of the darker and more abundant stained ground substance of ordinary silver-stained corneæ. The dark epithelial lines can be seen traversing the white groundwork, generally appearing to be interrupted when they come in contact with a stained patch of ground substance, and this usually prevents the completion of the visible boundaries of the cell out-

line. The interruption is, however, only apparent, the black line being lost in the dark mass which surrounds it, as may be seen when a patch is only slightly stained. The line can then be frequently traced over and beyond a dark island, completing the cell-contour.

Fig. 10 shows part of a successfully stained epithelial surface in the interior of a mouse's cornea, in which this continuation of the

Fig. 10.—Part of a layer of flat (epithelial) cells in the substance of a mouse's cornea Silver preparation.—Hartnack, Obj. 7, Oc. 3.

dark lines over the stained islands is in some parts visible. In the preparation there is another similar layer below the one represented, cornea substance intervening.

It is important to note that the cells indicated by the dark lines in Fig. 10 belong to a class of larger size than those of the layers of polygonal cells seen in the mouse's cornea in gold preparations.

The ordinary appearance presented by a cornea which has been treated by nitrate of silver, solid or in solution, is represented in Fig. 11.

In such a preparation the silver has completely permeated the substance of the fibrillary bundles. Wherever there is an uncoloured space, we know that the ground substance is wanting to an extent sufficient to be entirely out of focus. In other circumstances these spaces may be found filled with a black albuminate of silver. Sometimes a large unmistakable nucleus of the stellate cell can be seen in each space, establishing the relation between the cell and the space. But the space is larger than the cell, does not correspond to it accurately in outline, and the colourless

space-processes are very much broader than the processes of the stellate cell. It is evident that the silver permeating the fibrillary substance with ease, either does not readily find its way into the spaces, or if it does, that the spaces are bounded by a structure that does not stain by nitrate of silver. We have seen that it is possible to show the dark lines of epithelial cells in the walls of the spaces; and it is thus clear that either the substance of the cells does not stain, or that in such preparations the silver does not penetrate them. The fact of the dark lines being present would seem to show that there is a comparative difficulty of staining as regards the cells.[1] But that the epithelial layers in the

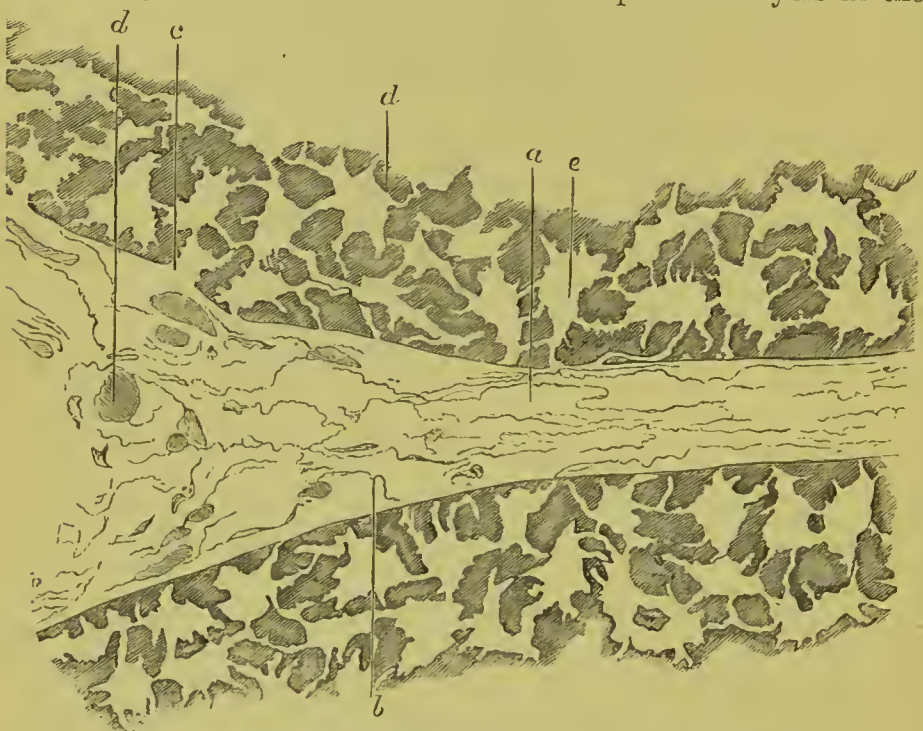

FIG. 11.—Section of a rabbit's cornea, stained by nitrate of silver.
a, Lymphatic vessel enclosing nerve.
b, Line between the epithelium.
c, Continuity of space with vessel.
d, Ground substance.
e, Space in which the stellate cell lies.

cornea form an obstacle to the passage of silver solution is shown by preparations obtained by placing the bulb entire in the solution for a few minutes, and subsequently removing the upper from the under layers of cornea substance. It is then often found that the silver solution has diffused itself equably through the whole

[1] Analogous cells can be stained in the subcutaneous tissue by an interstitial injection of silver solution, as can be shown by thus injecting the subcutaneous tissue of a mouse's back immediately after it has been killed.

of the fibrillary substance of one layer, but has not penetrated at all to the layer below it; from which I infer that a layer of flat cells in the cornea, and the delicate sub-cellular membrane on which such cells always lie, present an obstacle to the easy passage of fluid.

The demonstration of layers of flat cells in the cornea, and of an epithelium covering the spaces, shows that Recklinghausen was mistaken in supposing that the colourless stellate spaces and connecting processes are lymph canals (saft-kanälchen), channelled out of a substance which cements the fibrillary bundles. Each stellate space is formed by the superposition of lamellæ, one over the other, the surfaces being at points corresponding to the situation of the stellate cells, removed from each other to an extent sufficient to enable the distance to be appreciated under the microscope. In a silver cornea where the staining is pronounced, the distinction of the surfaces where they are in contact is lost to the eye. Thus, a "space" simply shows that two membranes, which are at other points in close contact, have at one point left a gap between them, and it is in these gaps that the stellate cells are to be found.

I have previously shown that the canals in which the nerves lie are lined by an epithelium, and are in reality large lymphatic channels, and, as will be seen by referring to Fig. 11, there are points in the lymphatic where the colourless spaces adjoining communicate with the uncoloured outline of the vessel. At these points it is certain that the fibrillary or ground substance fails, but it does not follow that the uncoloured breach in the outline of the wall of the vessel represents the extent of the actual free communication. That there is, however, a free communication at these points, between the lymph channel and the spaces, can be satisfactorily made out by watching the movements of bacteria in a cornea which has been placed in conditions favourable to their development. It can be seen that they move in the large lymph channel, but that at certain points one oscillating rod after another leaves the vessel and enters an adjoining space, and that always at the same point. When, as we shall afterwards see, white blood-corpuscles enter the inflamed cornea, they are sometimes found in considerable numbers in these lymph channels between the nerve and the wall of the channel, and it can then be seen that they make their way first into those spaces which are next the vessel. Whatever the nature of the communication may be—and it may not be more than a slight aperture at the angle of junction of the

epithelium of the vessel—it is sufficient to permit the passage not only of fluid, but of minute solid particles between the lymph channel and the spaces.

The structure of the cornea, as shown by the above histological methods, can be described shortly as follows:—The fibrillary or ground substance consists of parallel bands, whose breadth is nearly the diameter of a human red blood-corpuscle, and whose thickness is somewhat less than their breadth. These bands, which I have described for the first time, and which I call primary bundles, are covered by narrow, elongated flattened cells, after the manner of an epithelium. Injected masses can be made to pass between the primary bundles, the spaces into which they pass being the corneal tubes of Bowman. These tubes are not, therefore, canals, with a complete unbroken wall, but are the spaces left between the bundles, on account of the somewhat cylindrical or bevelled form of their borders. The walls of a corneal tube are formed by parts of the surface of several contiguous bundles.

The primary bundles are collected in larger bundles, and on the surface of these larger bundles are found layers of small flattened polygonal cells. The junction of the cells of the primary bundles with those of the secondary bundles shows that there is a continuous free surface for the passage of fluid from the surface of the layer into the corneal tubes between the primary bundles.

The secondary bundles are combined so as to form large flattened tracts, which are separated into distinct compartments by a membranous investment, which is covered by epithelial-like cells. If it were necessary to give these tracts a distinctive name, the term tertiary bundles might be applied to them. These are further arranged in layers, which can be appreciated by the naked eye, and the surfaces of which are covered by the larger cells shown in Fig. 10.

The flat cells of the cornea being thus arranged in layers, may fulfil all the functions which are usually attributed to the epithelium of a serous membrane.

Between the primary bundles are chains of very small spindle cells. They are entitled to the name of cell, notwithstanding their small size, because they are composed of a well-marked nucleus, surrounded by a small quantity of protoplasm. The processes of each cell anastomose with those next it.

In spaces left by the separation from each other of the laminæ,

formed by the bundles, are the large stellate cells, from the borders of which radiate in every direction, but mostly transversely and obliquely, a great number of transverse processes. The nucleus of this cell has formed the basis of the notions generally taught regarding the corneal cells. This nucleus and the surrounding spaces, filled with dark gold or silver deposit, constitute the appearances erroneously figured in the text-books as the corneal cell.

The processes of the stellate cells pass between the bundles of the upper and lower laminæ; and one result of this interlacing is the binding together of the bundles and laminæ. The anastomosing fibres penetrate between the flat cells at the angles constituted by their points of junction.

Fig. 12.—Transverse section of sheep's cornea, sealed in 10 per cent. salt solution.—Hartnack, Obj. 8, Oc. 3.

The bundles are thus woven into a texture by the stellate fibres. In Fig. 12 I have represented an appearance seen in a section of a cornea, sealed up in a solution of 1 part of common salt and 10 of water, which illustrates this relation between the stellate cells and the fibrillary tissue.

The circular apertures which are seen to form a margin round the shrunken cell, and under one of which a fibre dips to reappear through another, I have seen only in preparations thus sealed up in strong salt solution.

For the sake of readers who endeavour to reconcile my views with those expounded in the text-books, it is necessary to explain that the recognition of primary bundles, the flat cells which cover them, the spindle cells which lie between them, and the layers of small polygonal cells, has been brought forward for the first time in the papers I have lately published. The distinction between the large epithelium seen in silver preparations and the stellate cells, as different anatomical elements, is also new, and was first brought forward in the same papers. The establishment of these anatomical facts has been the result of several new histological methods, the wider application of which will, I believe, add much to our knowledge of the intimate structure of the tissues. Of these the chief are the isolation of cells by saturated solution of potash, the application of which will be further minutely described in the January number of the *Quarterly Journal of Microscopical Science*, in a paper on the Structure of Cartilage; the detection of elements *in situ*, which have hitherto escaped notice by simply sealing fresh

tissue in aqueous humour or blood serum, by running Brunswick black round the cover-glass, and examining the preparation from day to day ;[1] a more extended application of the same method of fixing cellular elements by gold solution, by which I was able to obtain preparations of flat cells in muscular fibre (*Edinburgh Medical Journal,* September 1874),—which is distinct from the ordinary staining by gold, and about which I shall have more to say in a future number ;—and the demonstration of the relations of the different kinds of cells to each other and to the tissues by a method of gold injection, imagined by Dr Ewart and myself, some of the results obtained by which we will describe in a paper on the Lens in the January number of the *Journal of Anatomy and Physiology.*

These methods applied to other forms of connective tissue yield results essentially similar to those described in regard to the cornea. The sciatic nerve of a frog, carefully cut longitudinally, and sealed in serum, shows, after a few days, sheets of polygonal cells which belong to the neurilemma, the existence of which has been previously demonstrated by Ranvier, in silver preparations. In the serum preparations I have further found, after twenty-four hours, isolated primary bundles, differing from those of the cornea only in being puckered transversely—the transverse puckering probably resulting from the less stable form of the tissue.

Fig. 13. — Primary bundle of neurilemma of the frog. Sealed serum preparation. — Hartnack, Obj. 8, Oc. 3.

I have further observed, within a few hours after the sealing of the preparation, lying isolated between the cut edges of the neurilemma, branched cells, with scant, finely granular protoplasma, and long slender glistening fibres—often of great length—which presented the objective characters of elastic fibres.

Fig. 14.—Branched cell from neurilemma of sciatic nerve of frog, isolated. Sealed in aq. hum. three hours.—Hartnack, Obj. 8, Oc. 3.

In the paper already referred to, I will endeavour to show that hyaline cartilage is composed of primary bundles, arranged in laminæ, which are covered by layers of flat cells, and that it is in spaces between the laminæ that the stellate cell (the ordinary cartilage cell) is found, and that there is no closed capsule, as has been generally supposed.

[1] See Proceedings of the Royal Society, No. 158, 1875.

Dr Ewart and myself, in the paper on the structure of the lens, will show that the lens fibres are covered by elongated flat cells similar to those which cover the primary bundles of the cornea, and that there are further layers of rounded cells which cover larger bundles of the fibres.

Fig. 15.—Cells from mesentery of a frog. Potash preparation. Hartnack, Obj. 8, Oc. 3.

In the mesentery of the frog, I have been able to isolate by potash solution a layer of small elongated narrow cells, similar to those described as being peculiar to primary bundles. Fig. 15 represents a few of these cells which formed part of a layer which nearly covered the field of a No. 8 objective of Hartnack.

To prevent any possibility of misapprehension, it is well to state that these cells have never been previously described, and that as yet I have not seen them, except in a potash preparation.

Essentially the same structure was explained as regards tendon in the paper published previously in this Journal; but it is necessary to revert to the subject in order to correct a misconception of my views, for which, as it has been shared by reviewers in the *Centralblatt* and *Revue des Sciences Médicales*, and by Professor Turner in his Introduction to Anatomy, want of explicitness on my part must be partly responsible. What I described as a secondary bundle has been understood to be the object I had in view when I used the term primary bundle. As far as I know, the distinct individual structure described by me as a primary bundle, has not been previously recognised. By turning to Ranvier's work, *Traité Technique d'Histologie*, p. 354, it will be at once seen from his figure (Fig. 119) what he means by a *faisceau tendineux;* and, as far as I can gather, the same object is what German and English writers have designated as a "bundle" of tendon. It is the somewhat conical or circular mass of tendinous substance, seen enclosed by the stellate spaces and their narrower prolongations, in a transverse section. The next element into which this bundle (faisceau) has been held to be resolvable, is the delicate ultimate fibrilla. But between this bundle or faisceau and the fibrilla I hold that there is demonstrable a definite uniform structure—a system of parallel flattened cylinders,—and it is a number of these placed side by side in close juxtaposition which form the faisceau or "bundle" of authors. In order to distinguish them from the ordinary "bundle," I termed them primary bundles.

Indications of these narrow primary bundles are seen occasionally by various methods, but frequently they are not seen at all

in preparations otherwise apparently good. They may be seen sometimes very distinctly in tendon sealed up in blood serum. A sealed preparation of tendon shows in a few days the ultimate fibrillæ with great distinctness, and for their demonstration I recommend this method in preference to any other, on account of its simplicity and certain success. But it can be further seen that these fibrillæ are arranged in parallel bands of a breadth approximating that of the primary bundles of the cornea, and that a number of these parallel bands compose the ordinary "bundle" or *faisceau*. One of the Ranvier cells covers transversely three or four of these primary bundles or bands, whilst, as is known, it only covers part of the ordinary "bundle," or what I call a secondary bundle.

I succeeded in breaking up a tendo Achillis of a nearly mature sheep fœtus into the primary bundles by long maceration in weak chromic acid, and at the same time the narrow elongated cells that cover them were, by a rare chance, preserved. These bundles and cells were described in my previous paper, and I repeat the figures that represented the preparations.

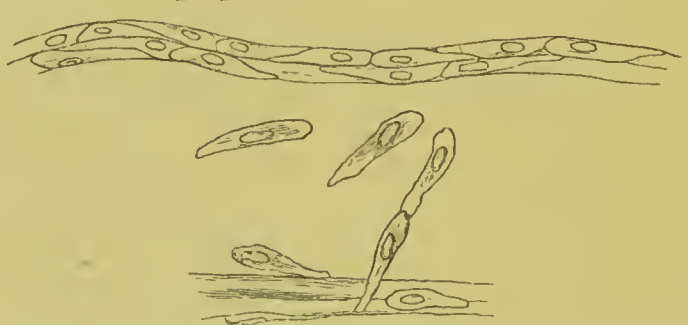

FIG. 16.—Primary bundles and their investing cells. Tendo Achillis of 14 inch sheep fœtus. Chr. acid.—Vérick, Obj. 12 (immersion), Oc. 1.

These figures, it must be borne in mind, represent the primary bundles and the cells that cover them, magnified by a No. 12 immersion lens of Vérick, with Oc. 1, and, I presume, therefore about 800 diameters.

The preparations are preserved in glycerine, and I have been able to demonstrate them to several anatomists and physiologists.

The same cells are seen in potash preparations, success in this instance being, however, rare; and also occasionally in sealed serum preparations. The two cells in Fig. 17 show their contour in a sealed preparation of the tendo Achillis of a frog, as seen by a No. 8 Obj. of Hartnack; and in order to show their relative size and outline in reference to the cells described by Ranvier, I place

beside it two of Ranvier's cells, as seen by the same magnifying power, in a preparation of the tendon of a mouse's tail, prepared as I shall presently describe.

Fig 17.—Cells of the primary bundles from tendo Achillis of frog. Sealed serum prep.—Hartnack, Obj. 8, Oc. 3.

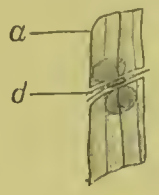

Fig. 18.—*a*, Cell of secondary bundle of tendon of mouse's tail (Ranvier's cells). *d*, Protoplasm and nucleus of a branched cell lying transversely between the two flat cells. Logwood-glycerine prep.—Hartnack, Obj. 8, Oc. 3.

From a series of measurements of the cells of the primary bundles in the preserved chromic acid preparations referred to, and of the Ranvier cells of the mouse's tail, I find that the cells of the primary bundles are equal in length to the Ranvier cells, but that the Ranvier cells are five times broader than the cells of the primary bundles. The nucleus of the cell of the primary bundle is a narrow elongated body, whose length is only a half, and breadth only a fourth, of the diameter of the nucleus of the Ranvier cell.

The breadth of the primary bundle is equal to the breadth of the broadest part of the cell which covers it. And to make any further misapprehension difficult, I may add that the primary bundle and the cell which covers it have not been described by any one but myself.

In my previous paper I described and figured the cells which form part of the membrane that covers the larger bundles (tertiary) of tendon. I did not figure Ranvier's cells, because I believed that they were sufficiently well known, but I described them as covering the bundles, in no respect differing in their nature from the more irregularly-shaped cells investing the larger bundles, or the smaller cells covering the primary bundles. Ranvier, in the *Traité Technique d'Histologie*, already referred to, has lately given an elaborate description of these cells, and teaches, not that they invest the bundles, but that they are arranged in isolated rows between them. Histologists will naturally settle this question for themselves in accordance with the results of their own observations.

I suggest the employment of the following methods, which are more simple, and succeed more frequently, than staining by gold, or by the other staining methods usually employed:—

The ordinary concentrated solution of extract of logwood and alum (not crystallized hæmatoxylin, from which it ought to be

distinguished) is filtered into glycerine drop by drop until the glycerine has become of a decided blue colour. Into this logwood-glycerine are placed the tendons of a newly-killed mouse's tail, and they are allowed to remain in it twenty-four hours or longer. They are then examined in glycerine. The bundles of fibrillary substance are unstained, but the substance of the Ranvier cells and their nucleus are stained blue, and are seen apparently arranged in rows. On altering the focus it will, however, be found that the rows first seen are lost, and others placed laterally to the former ones come into view. On careful examination, by judiciously changing the focus, it can, in successful preparations, be seen that there is no part of the bundles on which a cell cannot be observed. The cylindrical form of the bundle prevents any continuous layer being seen at one focus, but the lateral junction of the superficial with the deeper cells can be made out. The cells placed laterally on the bundle are seen most easily, because the light, in passing through them, traverses a greater depth of colour. Those on the surface lying nearly flat to the eye of the observer, can sometimes only be made out with difficulty, and are further liable to be injured by the cover-glass. Parallel longitudinal lines stained a deeper blue than the other parts of the cell—corresponding to the *crêtes d'empreinte* of Ranvier—are seen in the cells in such preparations. They are shown in Fig. 18.

In preparations by this method, there is often visible between the Ranvier cells an elongated nucleus—characteristic in form of that of a branched cell—from the scant protoplasm surrounding which a slender glistening fibre can be seen dipping downwards between the bundles. This nucleus is shown in Fig. 18, *d*.

Preparations demonstrative of the same facts can be obtained by sealing up portions of mouse-tail tendons in chloride of gold solution, care being taken that the tendon is kept stretched until it has been a few minutes in the fluid. The Ranvier cells and nuclei become gradually visible, and are seen well for twenty-four hours or longer. In the most successful preparations of this kind the elongated nucleus of the branched cell can be seen in nearly every interstice left by the borders of the Ranvier cells, and the flat cells, conspicuous by their nuclei, can be seen covering every part of the bundles. This latter mode of preparation succeeds most frequently, but the logwood-glycerine preparations are most demonstrative, and can be preserved. The cells can be seen on tendons that have remained weeks in the logwood-glycerine.

The staining and chemical solutions used in demonstrating the

cells of tendon, act most strongly on the cells adjacent to the wider channels between the bundles, because they not only penetrate to these cells most easily, but a larger interchange between the cell and the fluid is favoured by the retention of the latter in more considerable quantity than at the points where contiguous bundles are in contact. Consequently an incomplete staining is a frequent result, and we have then the appearance of cells arranged in rows.

In the next chapter I shall proceed to describe the changes that take place in these various elements when they are inflamed.

CHAPTER II.

The appearances seen in an inflamed cornea have been so much discussed of late years, that it might seem natural that I should begin by reviewing the controversy. I believe, however, that the majority of my readers will best understand what I have to say on the disputed points if I adopt the more systematic course of discussing in succession the changes which take place in the different elements which I have shown to exist in the cornea.

The phenomena of inflammation as they are seen in an injured cornea follow a certain sequence, modified by the extent and nature of the injury, and by the species of animal which is the subject of it. The rapidity with which the phenomena develop is subject to still greater variations. I attach therefore little importance to the exact number of hours or days after which they have been observed in any given case. The earliest and latest phenomena of inflammation may often be observed in one and the same cornea.

I have shown in the preceding chapter that the cornea substance is divided into tracts by clefts. These clefts become much more prominent in the inflamed cornea. They can frequently be well seen in the cornea of a frog after twelve hours' inflammation, produced by touching the surface with a fine point of nitrate of silver. The methods which I have employed for their demonstration are to seal the excised cornea in blood serum, or simply to treat it by gold solution in the ordinary way.

When the inflammation has been thus limited, the development of numerous well-marked clefts near the inflamed spot contrasts with their more sparing development in the parts of the cornea removed from the seat of inflammation. When it has been more intense, or has lasted a longer time, the cornea may be observed to consist in whole or in part of wide, well demarcated tracts, which are frequently parallel to each other. It can be seen in such preparations, that the double-contoured structures which form each side of what appeared to be a cleft are simply the lateral boun-

daries of contiguous tracts of cornea substance. Under the influence of the inflammatory change, these tracts are sometimes separated widely from each other, a cleft opening out as a wide gap, and in the floor of the gap can then be seen part of the upper surface of a subjacent tract. This separation of the component tracts or tertiary bundles (if this nomenclature be permitted) from each other is best seen when acute inflammation is rapidly produced.

Fig. 19 represents a small part of a large portion of the cornea of a frog, which was split into its component tracts in twenty hours by the inflammation produced by placing a drop of turpentine on the corneal surface.

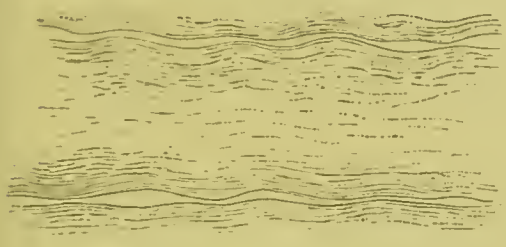

Fig. 19.—Separation of tracts of frog's cornea after twenty hours' inflammation. Turpentine. Gold preparation. Magn. 300 diam.

The examination of a number of corneæ has shown me that when the injury to the cornea is limited, the space over which this division into tracts is prominently seen is also limited. When, on the other hand, the injury has been produced by contact with some diffusible irritant, and the whole cornea has been inflamed, we find the division into tracts well marked over the whole structure.

That this division into tracts is not an accidental tearing is shown by the uniformity in its appearance, by the even borders of the tracts, and by its being only an exaggerated condition of what can equally be seen to exist in the healthy cornea.

In treating a healthy frog's cornea by a solution of purpurine, I have been lately able to observe the tracts and corresponding clefts developed to an extent almost equal to that seen in inflammation. Purpurine, a colouring matter extracted from madder, is a staining agent recently introduced by M. Ranvier,[1] to whose kindness I am indebted for the possession of the sample which I have used. My experience of it, although very limited, has been sufficient to show me that, in the study of the cornea, its use is attended with great advantages.

The significance of these tracts in regard to the phenomena of inflammation is best studied in a frog's cornea, in which inflammation produced by nitrate of silver has been limited to a very small surface, and the animal killed in twelve or twenty-four hours after-

[1] Archives de Physiologie, No. 6, 1874.

wards. The cornea should be left 20–30 minutes in gold solution and then exposed to the light in water acidulated by acetic acid until it has become well stained. The epithelium is removed with a brush or needles, and the cornea examined in glycerine. If the preparation is a successful one, the following appearances may be observed:—

From the cauterized part, recognisable by the usual appearance of the white spaces in a dark ground produced by silver impregnation, a broad tract of cornea substance, deeply stained by the gold reaction, passes towards the limbus corneæ. This tract on careful examination offers the following points for study: It contrasts with the cornea substance by which it is bounded laterally by the fibrillary tissue or ground substance being uniformly stained of a much deeper colour. In the dark tract, the purple black deposit in the spaces which indicates the position of the stellate cells is more abundant than in the other parts of the cornea, and is often in such quantity as to completely hide the stellate nucleus. Frequently, while there is this abundant metallic precipitate in the spaces of the inflamed tract, there is so little of it in those of the other parts of the cornea, that the position of the spaces in them can be made out with difficulty.

The lateral boundary of this darkly-stained inflamed tract may be formed either by a bevelled border or by a double contoured, perfectly colourless wall, which has an appreciable thickness, of an appearance resembling a section of Descemet's membrane in miniature. This colourless homogeneous border analogy justifies me in assigning to the membranous investment of the tract or tertiary bundle, seen perpendicularly, where it folds round the coloured fibrillary substance. The anastomosing spaces of each tract do not cross the border of this enveloping membrane.

It often happens that this limited darkly-stained inflamed portion of cornea dips downwards, and forms part of one of the middle layers of the corneal substance; and in this case, by alternately moving the focus upwards and downwards, homogeneous, slightly-stained substance can be seen above and below the inflamed portion, and bridging over the gap that bounds it laterally. The demarcation of the upper or lower layers from the inflamed one can be easily traced, because in the case of the former the anastomosing spaces can be seen unbroken laterally at the part corresponding to the boundaries of the latter, the spaces of the inflamed tract, as I have already stated, not extending beyond these boundaries.

This darkly-stained tract being continuous with the part of the

cornea injured by the caustic, and differing from the other parts by the abundant deposit of the gold chloride, teaches us two important facts in regard to inflammation, namely, that inflammatory change produced by injury at a given point may be propagated from that point along an isolated well-demarcated tract towards the nearest bloodvessels; and that further, in an early stage of inflammation, the nature of the fluid present in an inflamed tract differs chemically from that present in the surrounding uninflamed tissue.

The strength of this inference lies in the weight assigned to the reduction in the tissues of the chloride of gold in the form of a dark purple precipitate. I am unable to state what the substance is, the presence of which is necessary to the chemical action indicated by the precipitate. We know that it is unequally distributed in the tissues. It is notably present in ganglion cells, nerve fibres, and in the protoplasm which enters into the composition of stellate cells in some forms and stages of connective tissue. It exists normally to a certain extent in the lymph fluid of the tissues, and is always present in that of the cornea to a greater or less degree. But when it is present in an inflamed tract in larger quantity than in the uninflamed portions of the same cornea, it becomes certain that the lymph fluid in an inflamed tissue differs chemically from that usually present in the same tissue in a normal condition.

Observations by pathologists, made by other methods in other tissues, indicate that the change consists in the presence in the fluid of a fibrinogenic material, and the direction of the tract towards the conjunctiva indicates the nearest bloodvessel as its source.

Fig. 20 represents, as magnified by a low power, a preparation obtained by cauterization of the cornea of a winter frog (*Rana esc.*), which was killed twelve hours afterwards, and the cornea treated by gold.

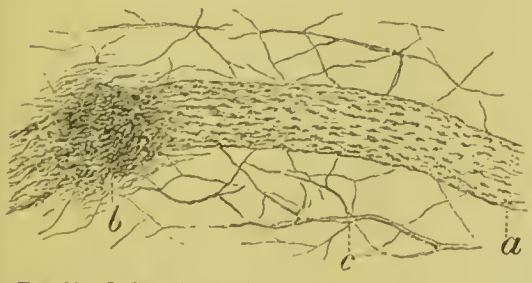

Fig. 20.—Inflamed tract in the cornea of a winter frog (*Rana esc.*), twelve hours after cauterization. Gold preparation. *a*, Border of tract. *b*, Cauterized surface. *c*, Nerve trunk.—Magn. 50 diam.

In the figure the dark diffused appearance resulting from the cauterization is shown at *b*. One of the borders of the inflamed tract is seen at *a*. The dark masses in the tract are the spaces filled by the gold precipitate. The rest of the cornea was scarcely stained at all, showing only the ramifications of the larger corneal nerves, one of which is indicated at *c*.

This important fact, so easy to observe, and so insusceptible of other than one interpretation, has in some unaccountable manner escaped previous observers. The inflamed tracts which I have been describing do not correspond to the "zones" described by some German authors as usually surrounding a cauterized part. The presence of an increased quantity of serous fluid in an inflamed cornea suggests that the separation of the larger bundles from each other is caused by the consequent distension, and not by any change produced in the fibrillary substance of which they are composed.

One of the most valuable and hitherto least regarded properties of chloride of gold solution is, that when brought in contact in certain conditions with the layers of flat cells, which I have shown exist in all connective tissues, these cells become fixed by the gold, and are more or less stained after they have been exposed to light in acidulated water. Mere contact of the solution with the cells is not sufficient to produce this effect, as is abundantly shown by the fact that the cornea has been saturated with the solution over and over again without the slightest indication of these cells being perceived. To produce the required effect it is necessary that the solution find its way easily between the layers, so as to come in contact with the cells on their free surface. The conditions requisite to secure this effectual contact may be obtained artificially by injection, and by various other manipulations suited to the different tissues operated on. One of the earliest effects of inflammation in connective tissue is a separation of the bundles by serous fluid—an acute œdema—and in consequence the gold solution finds its way between the lamellæ and stains the flat cells which cover them. A very short duration of the inflammatory process is sufficient to produce this effect.

Fig. 21.—Flat cells in a rabbit's cornea. Four hours' inflammation by alcohol. Gold preparation.—Magn. 400 diam. (See further in the text.)

Fig. 21 represents part of a preparation of a rabbit's cornea which had been irritated four hours before the death of the animal by the application of a few drops of methylated alcohol to the surface.

The cells thus stained by gold are seen in two different forms.

Most frequently they are arranged in rows which radiate from the central points in which the stellate nucleus is observed when it is successfully stained, the radiating rows from one centre being continuous with those from another, thus forming a broad network of epithelial-looking cells, enclosing colourless meshes.

At other times, in parts of the same cornea in which the radiating groups of cells are observed, cells similar in size and form are seen in broad layers. And transition stages can be found in which the rows of cells become gradually wider, until they pass almost imperceptibly into a broad unbroken layer of cells, with which they are continuous. Or the surfaces in the interior of the cornea may be so completely stained, that there are no radiating rows, the layer being stained continuously throughout.

In addition to the small polygonal cells of the rows and layers, the narrow elongated cells of the primary bundles are also sometimes stained by gold in an early stage of inflammation. They may be seen in the same preparations in which the polygonal cells are found, and then they can be observed in straight rows, one end of the row being in contact with a polygonal cell; the row passing into the fibrillary substance. In this case the position of the cells is similar to that seen in potash preparations of the healthy cornea, or to the aqueous humour preparation shown in Fig. 8; and it explains the direction taken by the injected mass in Schweigger-Seidel's injections.

Or, more rarely, the only cells stained may be those of the primary bundles. Fig. 22 represents a preparation of a frog's cornea in which the inflammation produced by scratching had lasted a few hours, and in which the gold solution was applied to the cornea, both before and immediately after the death of the animal. The only cells stained are those of the primary bundles.

Fig. 22.—Cells of primary bundles of a frog's cornea. Six hours' inflammation by scratching. Gold preparation.—Magn. 350 diam.

The rows of square cells shown in Fig. 21 at *a* have been seen by previous observers. In the *Wien. Medizin. Jahrbücher* for 1871, Hansen illustrates a paper on the changes produced in the cornea

corpuscles in inflammation by drawings in which anastomosing rows of flat cells with dividing nuclei are shown in the clearest manner. Stricker, in the *Jahrbücher* for 1874, in a paper on the suppurative process, gives a series of figures in which the same fact is amply demonstrated. I have had occasion to verify the accuracy of the observations of these authors; and even if I had not, Stricker's authority in such a matter would have been sufficient to remove any doubt. It is not in the observation, but in the interpretation of the fact, that I differ from that eminent pathologist.

My respect for the authority of Professor Stricker is so great, that it was only after long and careful study of preparations which, to my mind, admit of only one interpretation, that I ventured to dissent from his views. I owe too much to his teaching to have done so unadvisedly. But having been carried by the irresistible logic of facts far out of the track in which I started in the beginning of my investigations, I would now do neither Professor Stricker nor myself justice were I to attempt to write on inflammation without an examination of his published opinions. In the Vienna *Jahrbücher* for 1874, in the paper on the suppurative process, already cited, Stricker explains in full detail methods by which inflammation of the cornea may be studied. Appended to the paper is a Plate (Taf. XII.) which, if interpreted in the light of the views he holds regarding the normal structure of the cornea, shows at a glance the nature of the preparations on which his opinions regarding inflammatory change are based.

In the centre of the Plate (Fig. 5), a drawing copied from His of the "cell-network" of the cornea of a new-born infant shows a wide open network, in the central points of which a large nucleus is seen. The network is figured as of uniform appearance in every part. The narrowest parts are half the breadth of the broad central points; and there is no part narrower than the narrow diameter of the large nuclei. It is assumed, to start with, that this network is a cellular structure, in which the individual cells have not been "differentiated," or sufficiently separated from each other, to make it possible to say where one cell ends, and another begins. However, each nucleus is supposed to correspond to one cell, and the protoplasma of one cell is supposed to be continuous with that of the one next it. Imagine a field which is cut up by an irregular network of ditches, with a "stepping-stone" at each of their points of junction. According to Stricker's scheme, the field would be the cornea, the ditches anastomosing protoplasm (branched cells), and the stepping-stones nuclei.

Contrasting with this unbroken network, drawings are given of other networks as seen in the cornea of the cat when inflamed by nitrate of silver. These networks from the inflamed cornea, resemble those of the healthy cornea sufficiently to show that there is a unity in the two outlines, but the inflamed network is cut into a number of divisions which have the unmistakable contour of cells, and that they are undoubted cells, is shown by their containing nuclei, both entire and divided. To illustrate this by following out the simile of a field with a network of ditches, imagine the ditches divided into a great number of separate pools by dams, and the pools further irregularly subdivided, and in each separate pool one or more pieces of wood floating in the centre. The pools represent newly-formed cells, and the pieces of wood their nuclei.

Thus, according to Stricker, you have under the stimulus of inflammation a number of new or "young" cells developed out of a pre-existing one. The cells have "proliferated."

That the appearances observed are exactly as Stricker has described and figured them, can be easily verified. But the explanation he gives of them is irreconcilable with what we now know of the anatomy of the cornea.

To begin with, the "cell-network," given as the normal "cornea cells," is, as I have shown in the previous chapter, not a cell-network at all. It is a network of spaces formed by the separation from each other of two lamellæ, in such a manner that the visible contents of the spaces are seen in the reticulated form.

The cells that are seen in Hansen's and Stricker's preparations of inflamed cornea, are the flat cells that can be isolated by potash solution and maceration in aqueous humour from the healthy cornea. They are seen in inflammation as a network formed by rows of cells, because the silver solution then finds its way more readily along the channels between the laminæ than it can in the uninflamed tissue.

The part of Fig. 21 marked *a* is the same network seen by Stricker in silver preparations. His preparations were not, however, sufficiently successful to stain a large unbroken surface, such as that of which a part is shown at *c*. (In the simile of the field and ditches, *a* represents the pools into which the ditch is supposed to have become subdivided.) The belief in the existence of portions of cornea substance, such as that marked *b*, enclosed by a network *a*, is, however, founded on imperfect methods. The clear space *b* is in reality covered by cells similar to those at *c*, but they do not happen to have stained. The cells at *a* are not created by

the inflammation, but the inflammatory process permits their being stained.

The cells were there all the time, but were invisible. Once introduce the silver solution in a stream along their surface, and their contour is indicated by the characteristic reaction. In health it is impossible, or almost impossible, to secure the passage of the solution along the surface, but so soon as the laminæ are widely separated from each other by the serous effusion caused by the inflammation, the silver enters easily. It is like the discovery of the structure of the capillary bloodvessels. They were believed to be composed of a homogeneous membrane, until one day they were injected by solution of nitrate of silver, and a well-marked epithelium was immediately demonstrated.

Thus, in the inflamed cornea, the same cells figured by Hansen and by Stricker can be shown by gold solution; and if it does not succeed so often as the silver solution, on the other hand the preparations, when they are successful, are more instructive than those obtained by silver.

To recapitulate: in a gold preparation like that represented in Fig. 21, we find at one part anastomosing rows of cells precisely like those figured by Stricker and Hansen in their silver preparations; but more than that, we see what they did not find in their preparations, that at some parts the cells are in the form of a broad layer, and a faint indication of very slightly stained cells in the meshes of that part of the rows which is nearest the layer, shows that, whether we have a network or a layer, depends on the extent to which the solution has been able to pass between the laminæ, and that again depends on the extent to which the laminæ have been separated from each other by serous effusion.

All that preparations like those figured by Hansen and Stricker teach us is, that methods by which, in the healthy cornea, the layers of small polygonal cells existing in the tissue are not seen, are capable of demonstrating the same cells when the tissue is inflamed. Of "proliferation," or a formation of new cells, they give no evidence.

But such preparations assist us in studying the effect of inflammation on the flat cells which are thus made visible. It will be seen from Hansen's figures that the flat cells in his silver preparations contain small round bodies. These are products of a division of the nuclei. It will be also seen, on referring to Figs. 21 and 22, that a similar division of nuclei can be seen in gold preparations of the same cells.

It is an undoubted gap in this stage of the investigation that I am not able to describe the changes in these cells as seen in potash preparations, and one that I hope will be filled up by some other worker. The potash preparations succeed best in large corneæ; and in one or two that I tried, the reaction of the solution failed, and I have not since been able to repeat the experiment.

A more laborious, but more satisfactory, method of studying the changes in these cells than by the use of metallic solutions is to seal a properly prepared frog's cornea in blood serum. I touched the centre of the frog's cornea with a fine point of nitrate of silver, then neutralized the silver by a drop of salt solution, killing the animal after various intervals of time. In the sealed cornea, on the second to the fourth day, both the long and rounded flat cells could frequently be seen. In this way I have been able to examine cells at various distances from the injured part, which, in such preparations, is indicated by the dark silver groundwork and colourless spaces, and after the inflammation had lasted for various periods. The only change anterior to destruction of the cell which I observed was, that instead of one nucleus, there were two or more highly refractive spherical bodies, always smaller than what would have been the size of the original nucleus. The greater their number the smaller was each spherical body. Sometimes one or more such refractive particles were found in the body of the cell.

Fig. 23.—Flat cells in substance of a frog's cornea three days after cauterization. Sealed serum preparation.—Magn. 400 diam.

Of evidence of a division of one cell into two cells there was not a vestige.

It may be considered as proved, that in inflammation the nuclei of the flat cells divide. We shall afterwards see that the same fact holds good for the branched cells. What then? Shall we say that the first stage of a production of new cells has begun? No hypothesis more unwarranted by facts than this is, has ever taken root in the history of science. It has been the *ignis fatuus* of pathologists for a generation, and the idea has become so deep-rooted that it may even now appear to some rank heresy to call it in question. As, however, no one has ever seen the divided nuclei become the nuclei of new cells, and as it is desirable to limit discussion as much as possible to appearances which can be observed, I shall pass on to consider what we are taught by facts. One of the earliest effects of inflammation in the cells of connective tissue is, that the nucleus falls to pieces—disintegrates, not into

amorphous matter, but into component parts, the bond of union of which becomes weakened and gives way. The process is destructive, not constructive—is the first stage towards the death of the cell. Between the death of the one cell and the birth of another that may take its place, there is not a single fact to be observed that shows that the one is the parent of the other or of others. The question will occupy us again further on, but having had to describe the division of the nucleus, it was necessary, in order to prevent misapprehension, that I should state what I hold it does not mean.

Layers of small polygonal cells with a very large nucleus and a prominent nucleolus can be seen in the cornea of a mouse, after a few hours' inflammation by almost any irritant, if stained subsequently in gold; and such preparations are much more frequently successful in the mouse than in the rabbit. The cells thus seen in a mouse's cornea are only about a fourth the size of the large cells of the layer which can be demonstrated by silver in a mouse's cornea, and which have been shown in Fig. 10.

Similarly, much larger cells than those shown in Fig. 21 can be seen in silver preparations of the rabbit's cornea.

In a gold-injected cornea of a rabbit, into which incisions were subsequently made, and the cornea again placed in gold solution, and subsequently coloured in acidulated water, I saw at different parts of the cornea cells of both layers stained.

If a frog's eye, freed from the anterior corneal epithelium, be placed entire in half-per-cent. gold solution for an hour, and the cornea then excised and mounted in gold solution, the nuclei of all these cells can sometimes be seen.

Before discussing the changes that take place in the branched cells, I shall describe some appearances seen in the fibrillary tissue or ground substance which have not hitherto arrested the attention of observers.

In a cornea which has been inflamed by nitrate of silver, or by abrasion of the anterior surface, and then examined in serum, and especially in sealed serum preparations, portions of the primary bundles of various lengths can be detected on and near the injured part, and sometimes free in the serum. I refer the reader back to Fig. 1 for a representation of the appearance of these structures in the normal condition. When detached in inflammation, they present characters which are not seen in those isolated from the healthy cornea. Although of the same breadth, and distinguished by the same straight lateral contours, they differ from them in

being often seen to be cut by a straight transverse line. Like the blood-corpuscles, they are in serum preparations often found packed in the clefts between the larger bundles.

That the substance of which they are composed has undergone a chemical change, is shown by their appearance in gold preparations. They then stain a deep, almost black colour, and show transverse puckerings. Their condition when detached in inflammation is in some respects similar to that of the primary bundles of the neurilemma, and still more strikingly resembles the rods of the retina. This applies to the cornea and retina of the frog. I have elsewhere given my reasons for believing that the rods of the retina are simply one of the forms assumed by fibrillary tissue, and are in fact equivalent to primary bundles.

In osmic-acid preparations of a frog's cornea, which has been abraded for several days, parts of the primary bundles of considerable length are sometimes seen on the surface where the epithelium is wanting. They are even in contour and homogeneous in appearance.

When an abscess forms in the cornea as a result of acute and continued inflammation, if the cornea is treated by gold, large numbers of darkly-stained primary bundles can often be seen matted together with slightly-stained membranous substance, and numberless white blood-corpuscles.

I come now to a consideration of the changes that are to be seen in the stellate cells of the cornea.

The changes in the stellate cells are those on which the controversy in regard to inflammation has chiefly turned in Germany, and in order to avoid confusion, I ask those of my readers who are familiar with that controversy, to bear in mind the conceptions of the corneal cells entertained by the writers who have taken part in it. Stricker, Axel Key and Wallis, Cohnheim, and Böttcher, when they wrote their papers, believed that only one kind of cells existed in the cornea. Consequently, they discussed not what happened in one or another kind of cell, but in the "corneal cells." And as they did not all happen to have observed the same thing, we find a constant reference to discussions as to what the real nature of the corneal cell is. The true cause of the confusion to which all this has given rise seems to have dawned on Cohnheim, who in his last paper on the subject, entitled, "Keratitis Again!"[1]—a polemical essay directed chiefly against Böttcher and Stricker,—frankly confesses that too little is known of the anatomy of the

[1] Noch einmal die Keratitis, Virchow's Archiv, Band 61.

cornea to permit of a settlement of the question, and that "pathological histology has always been, and still is, a whirligig for every possible kind of speculation."

Nowhere has this whirligig of pathological histology gone more madly round than in the inflamed cornea. What has not been seen in it? Böttcher found that in three days all the branched cells had become spindles. Hansen had preparations in which there were crowds of pus cells, but not a single branched cell left, and others in which all the stellate cells had been washed into oblong forms by a stream. Cohnheim observed that when the corneal epithelium is wounded, the white corpuscles of the conjunctival fluid enter the wound, and, marching in goose step along the corneal lamellæ, halt, military fashion, at regular distances from each other, like soldiers on parade, and then become characterized by a newly-acquired spindle form. Truly a *Tummel-platz!*

If the views I have laid down regarding the anatomy of the cornea are borne in mind, it will be easy to understand how everything that has been described by Stricker, Cohnheim, Axel Key and Wallis, and Böttcher is perfectly consistent with them. Their descriptions and their plates correspond accurately with preparations that it is easy to reproduce, as it is only to be expected that they would. The opposite conclusions which have been drawn from these appearances have been due to want of sufficient knowledge of the normal anatomy, and not to any inaccuracy of observation. To this must be added a natural tendency to consider that what is not seen cannot exist—a habit that has been productive of much error in histology.

Not only the corneal elements, but those of most other tissues, are so absolutely transparent, and so perfectly alike in their refractive power, that the great object at which histologists aim, and in which they have as yet had very imperfect success, is to discover means by which these elements can be seen. It is seldom that any method succeeds in showing more than a part only of the elements known to exist. It has hence arisen that the opinions entertained by histologists on controverted points have depended much upon the methods they have been in the habit of using; and as histologists are generally not equally conversant with all known methods, and are severally apt to have an exclusive preference for those with which they are most familiar, it has come about that equally able and painstaking observers have come to very different conclusions.

In describing the changes I have observed in the stellate cell, I

shall be on common ground with other observers only as regards the nucleus. I cannot find that any one of them has ever seen the body of the cell except in one particular condition, occasionally seen in gold preparations, which I shall afterwards discuss; and if they have ever seen the processes, they have not distinguished them from other appearances, which they have erroneously described as the processes.

The nucleus of the stellate cell divides in inflammation, and divides at a comparatively early stage. I know two reliable methods by which this division can be observed. That of which I have most experience, is by gold staining.

Let a cornea, which has been inflamed a few hours or days, be placed in the solution for twenty minutes or longer, and then allowed to stain in the usual manner. A certain proportion of corneæ so treated will show the stellate nuclei stained a bluish slate colour. Frequently, and such preparations are best suited for this part of our study, nothing is stained but the nuclei and the nerves, with a more or less decided uniform reddish tinge of the substance proper of the cornea. The cell itself is absolutely invisible. If the irritant used has been some diffusible stimulant, such as alcohol, the nerves, especially in the frog's cornea, are often seen to their ultimate fibrillæ.

A certain number of such preparations will show that in some parts the nuclei have divided into two or more pieces. I attach little importance to the kidney form of the nuclei, as it is often seen where there is no pretence of inflammation. But there are other forms, which are certainly stages of division. A line sometimes cuts the nucleus obliquely through the centre, leaving the two parts joined by a narrow border. In others, a projecting corner, or a lateral portion, is almost severed from the body of the nucleus. Then we find adjoining these forms, instead of one large nucleus, irregular fragments of what had evidently been a nucleus. And it is nearly always evident that, if the fragments could be placed together again, they would constitute a body of similar size and form to the undivided nuclei near them. Occasionally, instead of a nucleus or parts of a nucleus of appreciable size and form, there is a shapeless granular mass of large particles resembling in colour the stained surrounding nuclei.

These fragmentary portions of a given size, I know to be parts of a nucleus, when I find them in a preparation in which the nuclei are equally stained throughout the whole field; when two or more portions occupy a position that would, according to the dis-

tribution of nuclei over the field, be occupied by one; when the portions correspond in colour with the undivided nuclei; and when, further, they do not belong to flat cells, spindle cells, or to white blood-corpuscles,—the only structures with which it could be imagined that they might be confounded. We shall afterwards see that these last can be identified, when they are present, by special characters which they possess.

Fig. 24 shows characteristic forms of the stellate nucleus, divided in inflammation, when treated by gold solution.

Fig. 24.—Stellate nuclei, entire, dividing and divided. From a frog's cornea, five hours inflamed by mustard. Gold preparation.—Magn. 400 diam.

Böttcher represents a similar appearance in one of his plates.

In my experience the demonstration of the division of the stellate nuclei by gold has not often succeeded, and when it has, the division has extended only over a very limited area. The changes in the spindle-cells, which I shall afterwards describe, take place over an area much more extensive.

Another method of demonstrating the division of the stellate nuclei consists in staining by purpurine—the dye extracted from madder, the uses of which in histology have been lately described by Ranvier. It has the advantage over gold that it succeeds with more certainty. Its results, in regard to the nucleus, are quite as demonstrative and beyond question as those obtained by gold, but are not more so. M. Ranvier lately showed me a frog's cornea in which the division of the stellate nuclei in inflammation was shown by purpurine-staining in the clearest manner. The method and the preparations obtained by it will be found described in the paper referred to. He pierces the cornea of a frog by a needle, and on the second and third days thereafter inserts the needle into the original aperture. On the fourth day the frog is killed, and the cornea is stained in purpurine. The nuclei of the stellate cells are uniformly stained a very pale rose, and their outline is seen to correspond to that seen in gold preparations. In the vicinity of the spot through which the needle was passed, instead of one large nucleus occupying the position relative to the other nuclei in which a nucleus is to be expected, two or three portions of a nucleus are to be seen lying near each other. The eye can readily judge that

the aggregate size of the pieces does not exceed that of an undivided nucleus. In the neighbourhood of these separated portions nuclei can be seen in a partly divided condition. No one can look at M. Ranvier's preparations, or the gold-stained ones I have described, and afterwards doubt that the nucleus of the stellate cell can divide. But it is evident to me from the same preparations that the division is nothing else than a disintegration. The nucleus has fallen to pieces which are not amorphous, but have, at least for a time, a definite contour and individuality.

The products of division in M. Ranvier's purpurine preparation were round. In the gold preparations I have always seen them angular. This difference I attribute to the mode of preparation.

What is the significance of this division of the nucleus of the stellate cell? By some histologists a division of the nucleus will be deemed conclusive proof of the birth of a progeny of new cells —"proliferation." But of this there is not a trace of evidence, nor can any appearance be seen which makes it even probable. If we keep strictly to the facts, it will be found that nothing has been observed, and therefore nothing is known of the future history of these bits of nucleus. There are no young cells, or wandering cells, or pus cells, in the inflamed cornea, other than white blood-corpuscles; and, as we shall see in a future chapter, there are methods by which white blood-corpuscles can be accurately recognised in the cornea. If any one studies carefully the appearance of a fragment of separated stellate nucleus, and compares it with that of a white blood-corpuscle, he will come, I believe, to the conclusion that a transformation so great as is implied in believing that the one is derived from the other, must present transition stages. No such transition stages have been observed. "Pus cells" in an inflamed or suppurating cornea are indistinguishable from white blood-corpuscles, and constitute a definite recognisable structure, the unity of which, as we shall afterwards see, can be established by several distinct methods. By none of these methods can products of a divided nucleus be seen to constitute or approximate in appearance the white blood-corpuscles in the tissue.

Equally unfounded is the idea that, when one such nucleus divides into two or three portions, each portion becomes the nucleus of a new or "young" cell, similar to that to which the original undivided nucleus belonged. Nothing has ever been seen which would favour even the probability of any such hypothesis. If we confine ourselves to facts, we cannot get beyond the simple one that the nucleus falls to pieces—divides. The theory of "pro-

liferation" that has been founded on this fact was at one time a fair and reasonable hypothesis. As a hypothesis, it has however remained utterly unsupported by evidence, and now lives only as a superstition. No other term can appropriately describe a belief in which faith counts for everything, and evidence nothing.

If I am asked what becomes of the separated portions of nucleus, I confess my ignorance. That they undergo further disintegration, degeneration, and absorption, is, however, a supposition consistent with what we know of the changes that take place in the elements of tissues whose vital conditions have been disturbed.

If we leave the nucleus, and come to a consideration of the changes that are observable in the protoplasm and processes of the stellate cells, we come to a field in which I find little to criticise in the writings of the German authors whose names I have so frequently had occasion to mention. A condition in which the cell in the inflamed cornea is seen in gold preparations as a dark spherical body, with distinct contours, is, I believe, that which is represented in Fig. II. of Taf. I. of Stricker's *Studien*.[1] But in the other figures of the plate, and in everything else that I have seen figured, and which has been described, I can find nothing that I can recognise as belonging to the stellate protoplasm or processes. Masses of white corpuscles, nuclei, and portions of separated flat cells, and spindle cells, comprise the mass of what have been believed to constitute products of the inflamed stellate cell.

The stellate cell and processes may be sometimes seen in sealed aqueous humour preparations, or when the cornea is placed in half-per-cent. salt solution. But I have not often found such preparations sufficiently distinct throughout to be reliable. All that I have learned of the stellate cells, has been seen in gold, and more especially in osmic-acid, preparations.

In an inflamed cornea, and in my experience much more frequently in the rabbit's cornea than the frog's, gold preparations sometimes show the dark spherical bodies to which I have already referred. Their distribution in the cornea corresponds to that of the stellate nuclei, but I have seldom been able to observe a nucleus in them; on rare occasions, however, I have seen a nucleus. The contour of these bodies is sharply limited, and I consider their nature is sufficiently established by preparations which I shall now describe. Before leaving them, however, I have to add that they are most frequently seen in a cornea which has been acutely in-

[1] Studien aus dem Instit. f. Exp. Path. in Wien. Vienna, 1870.

flamed by the application to its surface of some diffusible irritant.

I have several times obtained preparations in the inflamed cornea of a rabbit treated by gold in which structures were visible which I could identify with certainty as the stellate cells and processes. They are unlike anything that has been hitherto described or figured. Spherical bodies stained very darkly communicate with each other by fine dark lines on which are globular swellings or varicosities. The spherical bodies forming the centres of the network are similar in size and appearance to the isolated spherical bodies previously described, some of which can generally be seen at another part of the field; and that they are identical in nature, is shown by an intermediate zone in which a sphere has only one or two short isolated proeesses.

This network I have found in the superficial laminæ of corneæ which had been acutely inflamed by the application of alcohol. The preparations were obtained not by section, but by detaching the layers with forceps, a procedure which was facilitated by the action of the very dilute acetic acid to which the cornea was transferred from the gold solution. In the few instances in which I have seen this appearance I have found it extending only over a very limited area, and immediately adjoining it were seen the stellate nuclei and the meshes of the corneal spaces, indicated by an abundant black metallic deposit. Fig. 25 shows this network of inflamed stellate cells.

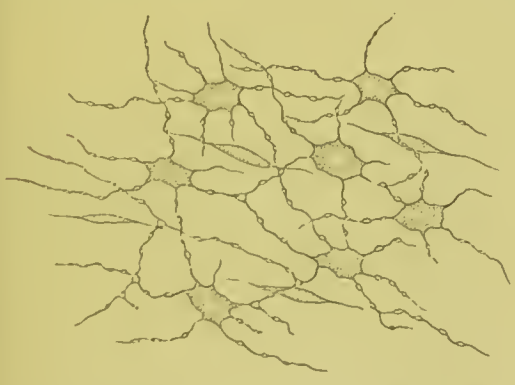

Fig. 25.—Stellate cells and processes from a rabbit's cornea, four hours inflamed by application of alcohol to the surface. Gold preparation.—Magn. 350 diam. (By mistake the varicosities have been engraved as spaces. They should have been dark throughout.)

In osmic-acid preparations of the inflamed rabbit's cornea, I have been able to see exactly the same appearance, and in them its nature could be better studied.

Several rabbit-corneæ that had been inflamed a week by a thread, were placed twenty-four hours in half-per-cent. solution of osmic acid, and thin transverse sections were then made without further preparation and examined in glycerine. In the majority of these sections, swollen spindle cells, and great numbers of white blood-corpuscles and newly-formed vessels can be seen.

In some of them, where the section is very thin, the stellate cells and their processes become visible. If the section is stained with red aniline, the cells are made much more distinct, and by a double staining with red aniline and logwood the nuclei are also well seen. No one who looks at such a preparation (and I have shown similar ones to several competent observers) can ever afterwards confound the stellate cells with spindle cells or white blood-corpuscles.

It is common to find the stellate cells unaltered in sections which show many swollen spindle cells and many white corpuscles. The stability which the stellate cells manifest when compared with the spindle cells, is very striking. By this method it can be shown that a part of the cornea may be undergoing important changes, and its interstices filled with white corpuscles, and yet the stellate cells and processes be unchanged.

But it sometimes happens that at one particular part of the section in an osmic-acid preparation, the stellate cells and processes have undergone a change. The body of the cell, instead of showing the characteristic lateral curves and projections which indicate the stellate form, has become spherical. Although its width is less than in the unaltered cells in the same preparation, it can be seen that the cell has increased in thickness. From a flattened it has become a globular body, and from its circular contour the processes project abruptly. The processes, instead of being fine, even, double-contoured fibres, like those of the neighbouring cells, present slight dilatations at regular intervals. The altered cells and fibres anastomose with the unaltered ones next to them. Such a preparation is more satisfactory than a similar gold preparation, because the unaltered stellate cells can also be seen, whereas in the gold preparations the altered cells are alone visible.

In a rabbit's cornea, inflamed by a thread, this appearance in osmic-acid preparations is only rarely seen. Whether it would be seen more frequently in osmic-acid preparations of a cornea, acutely inflamed by alcohol—the conditions under which I found it in gold preparations—I do not know.

A drawing of an osmic-acid preparation of these stellate cells shows that there is no difference between it and the gold preparation drawn in Fig. 25, except that of colour. It is therefore useless to give a representation of it, except in coloured plates.

The fibres of the cells shown in Fig. 25, both in the preparation and the drawing, are in some respects so like certain nerve fibres seen in gold preparations of the cornea, that for the sake of those

who are not intimately acquainted with the appearance of the corneal nerves, it becomes necessary to show that they are not the same. An opinion originally put forth by Kühne, and recently revived by Thanhoffer,[1] that the nerves and processes of the stellate cells are one and the same structure, makes this the more necessary.

In gold preparations in which the nerves are well seen—and this is only the case when the very fine ultimate fibrillæ, which can be seen by no other than the gold method, are visible—the final termination of the nerves is observed to be in exceedingly delicate beaded threads, which run mostly in straight lines, crossing each other in different places, and joining each other at central points. These fibrils, if carefully traced, are often seen, after running quite straight for a considerable distance, to bend round and take a direction at right angles to their previous course. One fibril often joins another at a right angle, their junction representing that of the limbs of the letter T. They can be recognised by their exceeding fineness, their beaded appearance, their being mostly in straight lines, and in a very successful preparation by their number, which is great. The discovery of this property of chloride of gold, to which science is indebted to Cohnheim, has been of incalculable value in studying the nerves, and its uses in this respect are still far from exhausted.

Fig. 26.—Nerve fibrilla crossing stellate nucleus in a frog's cornea. Gold preparation.—Magn. 400 diam.

Most excellent and instructive drawings of the corneal nerves have been given by Dr Klein in the *Quarterly Journal of Microscopical Science* for October 1871. Dr Klein has also pointed out a fact, which must often have been confirmed by students of the inflamed cornea, that the best nerve preparations are obtained when the cornea has undergone a slight amount of inflammation—a fact no doubt due to the easy penetration of the solution being favoured by the resulting serous effusion.

Fig. 26 shows only sufficient of the appearance and course of

[1] Virchow's Archiv, 63 Bd., 1 and 2 Heft.

these ultimate nerve fibrillæ, as is necessary to contrast them with the stellate processes in Fig. 25. English students who wish to see more complete drawings, may refer to Dr Klein's papers. They can also easily obtain preparations for themselves, from the cornea of a frog or mouse, in which a slight amount of irritation has been produced for a few hours, the excised cornea placed a quarter of an hour in gold solution, and then allowed to colour in faintly sour water. The chief condition of success is a certain amount of serous effusion. As the cornea can be examined entire in glycerine after the removal of the surface epithelium, the manipulations are exceedingly simple.

These fibrillæ differ from the inflamed stellate processes in gold preparations, in being more delicate, in their parallel and rectangular course, and in their complete isolation from the stellate cells and nuclei, which can be made out with absolute certainty in preparations that have been sufficiently successful.

The Hungarian Academy has published a series of twelve coloured plates, illustrating with great detail and beauty Dr v. Thanhoffer's views regarding the structure of the cornea. Copies are sold at a merely nominal price. One of these plates illustrates the nerves of the cornea.

In this plate, surrounding the stellate nuclei there can be recognised the usual metallic deposit, extending in narrowing projections between the bundles. In the plate the fine nerve fibrillæ can be seen to terminate in these projections. From such preparations Thanhoffer has concluded that the nerves end in the stellate cells.

But better preparations, such as those figured by Dr Klein (and I have, during the last eight months, frequently obtained similar ones), show that the nerve fibrillæ do not terminate in those projections as they seem to do in less successfully stained corneæ. They enter the space, pass under, over, or through the less darkly stained granular mass, as an unbroken thread, and are continued beyond it, either in a straight line, or turn round in the space and leave it at an angle (frequently a right angle) to their former course.

Another class of preparations demonstrative of the same fact, are those in which the granular mass in the space is invisible, and in which nothing is stained except the nuclei and the nerves. The nerve fibril can be seen taking a straight course to the nucleus, and as it is not concealed by any other stained substance, it can be followed passing close to the nucleus, and then frequently changing its direction. Its complete independence of the "space" or anything that is contained in the space, is in such preparations put

beyond question. One such fibril and nucleus is shown in Fig. 26.

It is evident to me from his plates, that v. Thanhoffer has never seen a process of a stellate cell, nor can I recognise any part of his drawings as being like the cell body. But if more proof be wanting that Fig. 25 does not represent nerve structures, it is found in those osmic-acid preparations which show a similar appearance. Osmic acid stains the medullated nerve characteristically. It is only in very exceptional instances that it stains the ultimate nerve fibrillæ at all. I am not aware that any one has ever seen the ultimate nerve fibrillæ of the cornea in other than gold preparations.

In an osmic-acid preparation, from which a drawing similar to Fig. 25 was made, and in similar ones still preserved, there is not a trace of nerve structure visible.

Further, Fig. 25 corresponds to the distribution of the stellate cells as ascertained by the methods explained in Chapter I.

Having thus shown that Fig. 25 represents the stellate cells and processes, there are two facts connected with the preparation that call for remark.

First, there is the curious one, that the processes of the cells and the cells themselves, otherwise invisible in gold preparations of the cornea, are now seen so darkly stained. The dark colour produced here by the gold, is similar to that seen in the scant protoplasm which surrounds the nuclei of stellate cells in gold preparations of the skin. The fibres of such cells, when seen at all in gold preparations of connective tissue, are usually pearly white.

The hypothesis which I suggest explains the staining of the inflamed cells and processes in the corneal preparation is, that there is in the cell and within the processes an albuminous fluid, which is not present in the uninflamed tissue; and I infer from this appearance, that there is a communication between the cells and the interior of the processes, in analogy with a similar fact that can be shown for many elastic fibres.

The varicosities on the processes must, from the regularity of their appearance, be considered as corresponding to peculiarities of structure.

I have not been able to trace any further change in the stellate cells in inflammation. I have not recognised them in the débris of the cornea when broken down by the morbid processes, nor have I seen them undergo any change that would point either to their giving origin to a progeny of pus corpuscles or "young cells" of

any kind whatever, or that they themselves undergo any organic transformation.

An account of Mr Lister's interesting observations on the movements of pigment granules in the inflamed web of the frog's foot, which from some points of view should find its place here, will be discussed further on in another connexion.

In the next chapter I shall discuss the changes that take place in the spindle cells in inflammation.

CHAPTER III.

Spindle-Cells and Colourless Blood-Corpuscles.

The spindle-cells in the cornea are, as I have already stated, exceedingly difficult to observe in the healthy tissue. In the inflamed cornea, on the contrary, they are usually very prominent objects. This depends partly on the fact, that in inflammation their protoplasm becomes more granular, and their nuclei are more susceptible of staining.

Accordingly, whilst I am not aware of any author having described them in the healthy cornea, their existence in which has been overlooked, I have found appearances described by nearly all the authors who have lately written on the inflamed cornea, which I can without any violence apply to the inflamed spindle-cells. Some of these writers, indeed, have described them unequivocally as spindle-cells, formed during the inflammatory process by a metamorphosis of the stellate cells.

A brief reference to these notices will have a special interest for some readers, and will be useful to those who wish to study the literature of the subject for themselves.

This account is, of necessity, incomplete, and its arrangement is determined by the order in which the writings referred to happened to be accessible to me.

Norris and Stricker[1] describe the "cornea-corpuscles" of the frog after a few hours' (in den ersten Stunden) inflammation produced by cauterization with nitrate of silver as being "either flat and having several processes, many of which divide, or as oblong and spindle-shaped."[2] "This last form," they remark, "is often extraordinarily prevalent, at other times it is scarce. We have met with it in the vicinity of the eschar, and at the periphery of the cornea, near the pigment. The spindle elements are sometimes

[1] Studien, page 3.

[2] The term "spindle-cells" here, and already so often used, is equivalent to the "fusiform cell" of many English authors.

single, at other times accumulated in groups, which are arranged in two directions which cross each other at a right angle."

Again,[1] describing a cornea in which inflammation had been produced indirectly by a thread passed through the bulb, the cornea being excised and treated on the second day by chloride of gold, the same observers remark, "We find on the periphery of the cornea, a part equal in extent to the whole field, in which there is nothing but spindle elements, which are arranged in two directions at right angles to each other. The protoplasm of these cells is relatively scant, and they contain invariably two or three rounded nuclei."

Kühne is cited by Stricker[2] as having seen on the border of a frog's cornea, which he had mechanically irritated, stellate corpuscles become spindle-shaped.

Recklinghausen[3] states that in the inflamed cornea he found two kinds of cells, which he did not find in the healthy cornea, namely, migrating cells, larger, and moving more slowly than similar cells which are seen in the healthy cornea, and spindle-shaped cells having fewer processes than the "fixed" cells, sometimes rounded at at one end and having a process at the other. These, he suggests, may be a transition form of "fixed" cells which are becoming movable.

Hansen[4] states that in the inflamed cornea he saw "transition forms, from undoubted cornea-corpuscles to elongated perfectly spindle-shaped structures, which are to be considered as having reached the extreme degree of change of form." He also frequently found parts of the cornea where there was "not a single normal cornea-corpuscle remaining, the whole field being filled with small oblong bodies crossing each other." He suggests as a possible cause of this supposed change of form, that the "corpuscles" are acted on by a stream which, passing through the cornea, washes them into the interfibrillary spaces, whose arrangement in parallel and crossing layers they accordingly assume.

Böttcher,[5] instead of nitrate of silver, used chloride of zinc, and when he cauterized a limited point in the centre of a frog's cornea by this irritant, he succeeded in producing inflammatory changes, which were independent of any change that proceeded from the conjunctival vessels next the corneal border. As part of the process by which these changes were produced, he believes that in three days all the stellate cells had been transformed into spindle cells.

[1] Loc. cit., p. 11.
[2] Handbuch, p. 14.
[3] Eiterung, etc., Virchow's Archiv, Bd. 28, p. 180.
[4] Wien. Med. Jahrb., 1871.
[5] Virchow's Archiv.

We shall see further on, that the same structures described by the above-named authors as spindle-cells derived from the "cornea-corpuscles," have been seen and described by Cohnheim and others as colourless corpuscles in spindle form.

Both schools agree in believing that the spindle-shaped structures arise, *de novo*, as a result of inflammation, but the one believes that they are transformed, pre-existing elements; the other, that they are peculiarly-shaped, colourless blood-corpuscles, which have entered the cornea from the nearest bloodvessels.

The strictures of the one of these schools on the views of the other are in both instances so well-founded, that it seems to me that the controversy must last as long as the views which have been hitherto held regarding the structure of the cornea hold their ground. As these have already lasted long enough to establish a kind of prescriptive right to a place in text-books and prelections, they will probably die hard, and no one can tell how many successive generations of students may yet hopelessly struggle with "spindle-shaped bodies," "dagger-like figures," and "negative and positive images."

I have previously shown that it is possible to see in the healthy cornea, chains of minute spindle-cells with fine connecting processes. These correspond in number, in arrangement in parallel rows, in the fact that the rows in one plane cross those in another, and in the relative distance of the nuclei from each other, with the spindle-shaped bodies seen in the inflamed cornea. The presumption, therefore, that they are the same is so strong, that almost the only proof required is that of the existence of spindle elements in the healthy tissue. To demonstrate them in health, requires as we have seen, the employment of special methods.

In the inflamed cornea, they can be seen by several different methods. Those chiefly employed during late years, have consisted in examining the freshly excised cornea in aqueous humour, and in staining with gold. Norris and Stricker, for example, have described spindle-cells seen in a cornea, examined in aqueous humour after a few hours' cauterization. I have found, however, that they can be seen more distinctly, and their relation to the other elements of the cornea better understood, if the excised cornea is sealed in aqueous humour or blood-serum, and examined after 24 to 48 hours.

My best preparations were obtained in the following manner:— Choosing a large frog (*Rana esc.*), I touched the centre of the cornea with a fine point of nitrate of silver, and immediately

neutralized the caustic by placing a drop of half-per-cent. salt solution on the eye. In winter, all inflammatory changes in the frog proceed more slowly than in summer, and in the esculent frog, more slowly, I think, than in the common English frog (*Rana temp.*). I therefore made a series of experiments in winter on the large Continental variety. The conditions in which I happened to be placed, made it inconvenient for me to examine the cornea at other than invervals of twelve hours after cauterization, which is the only reason why the first changes I describe are those seen after the first twelve hours. I have also, at other times, examined frog corneæ after various much shorter intervals, but I have found nothing which makes it necessary to describe them further.

In a cornea treated as I have above described, sealed in serum, and examined after twelve hours, the following points may be observed if the preparation has been a successful one. Adjacent to a part in which the corneal epithelium is wanting, there may often be seen a part in which the contours of an epithelial layer are marked by the ordinary dark network generally observed in silver preparations. The epithelial cells have been affected by the silver, and are much more easily seen than the epithelium on other parts of the cornea. In the part which has been denuded of its epithelium, there can be detected, by careful examination with a magnifying power of 300 or 400 diameters, oblong, shuttle-shaped bodies, arranged in rows, and maintaining generally a somewhat constant distance from each other. Their greatest breadth approaches roughly that of a human red blood-corpuscle, and their length is about a half more. They are composed of a colourless, very finely granular substance, the appearance of which justifies the application to it of the general term protoplasm. A more careful examination enables us to detect in the protoplasmic mass one or more elongated nuclear bodies, and at either end a fine process, which is continued into a similar adjoining protoplasmic body. Each mass, consisting of a nucleus (or nuclei) protoplasmic substance, and terminal processes, constitutes the histological element known as a spindle (or fusiform) cell. The protoplasm, scant in quantity at the centre of the cell, is continued for a very short distance into the process. The processes are seen as fine cylindrical thread-like structures, whose refractive properties differ considerably from those of the cell-substance. The arrangement of the cells is in rows or chains, parallel to the direction of the bundles of fibrillary or corneal substance, and to each other.

Fig. 27 represents part of a preparation, such as those which have formed the basis of this description. The epithelium is seen slightly acted on by the nitrate of silver, and where it is wanting are seen the chains of spindle-cells and processes above described. The figure gives a good idea of the relative size and position of the cells and processes, but it is impossible in a woodcut to represent accurately the peculiar refractive properties which characterize them. In successful preparations, their individuality is more evident than it is possible to show in an engraving.

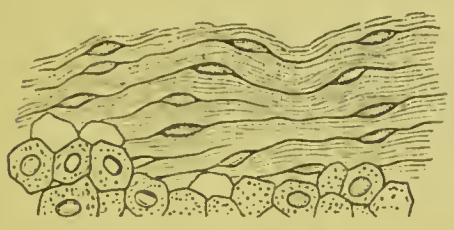

Fig. 27.—Part of a frog's cornea (*Rana esc*) twelve hours after being touched by a fine point of nitrate of silver. Sealed serum preparation. Drawn after the cornea was forty-eight hours sealed. The spindle-cells are at one level and are parallel to the transverse plane of the cornea.—Magn. 400 diam.

It can sometimes be seen that the chains of spindle-cells are visible in a corneal tract, while they are not seen at all at the other parts of the structure. In such cases, the visible spindle-cells can be traced to the border of the cauterized spot, and the area in which they are visible is bounded by one of the walls of a cleft. On the other side of the cleft, there may be no evidence of their existence. The tract in which they are seen is such as has been shown in Fig. 20. The preparation from which the drawing there represented was made, if it had been sealed in aqueous humour, instead of having been treated by gold solution, would probably have shown in the inflamed tract, instead of the dark areas of metallic deposit, chains of spindle-cells similar to those represented in Fig. 27.

The fact which this method teaches us is, that in inflammation the spindle-cells and processes have undergone a change, causing their refractive properties to differ from those of the tissues amongst which they are situated.

The inferences derived from sealed preparations acquire certainty by comparison with osmic-acid preparations, in which we more particularly get accurate notions regarding the increase of the protoplasm in the cells.

I have used this reagent for this purpose principally in the cornea of the rabbit. A thread was passed through a portion of the cornea, and the animals killed at periods of one, seven, twelve, and fifteen days. The cornea was then excised, and placed in a half-per-cent. solution of osmic acid for twenty-four hours. Sections can then be made without further preparation, but as it is desirable to have as many sections for examination as pos-

sible, I have usually divided the cornea into several pieces, which I imbedded in wax and oil, to facilitate cutting.

In a cornea which has been inflamed for only twenty-four hours, sections can be obtained in which the even homogeneous ground substance is broken by elongated, spindle-shaped, protoplasmic masses, widest at the centre, and tapering to a point at either extremity. The protoplasm, stained by the osmic acid more darkly than the ground substance, is coarsely granular in such sections. In the thinnest sections, it is possible to trace a very fine fibre connecting the contiguous extremities of the spindle-shaped masses. If the section is stained in logwood, two to four—generally four—small nuclei are seen in the centre of the protoplasm. The arrangement of these small nuclei is invariably in a row. They are never grouped in a cluster, and in this respect they differ from the nuclei of the white blood-corpuscles. As an important point in making the diagnosis between spindle-cells and other structures with which they may be confounded, I lay great stress on this linear arrangement of the divided nuclei.

(*a*) (*b*)

FIG. 28.—Spindle-cells from inflamed cornea of a rabbit. Osmic acid. Logwood.

a) Increase of cellular protoplasm. Nuclei entire. (*b*) Nuclei divided. Magn. 400 diameters.

In sections of a rabbit's cornea, which had been twelve days inflamed, I found in the position of the spindle-cells, near the corneal border, at a part removed from the chief seat of inflammatory change, long protoplasmic columns, presenting slight constrictions, and containing nuclei in their interior. The distance of the nuclei from each other was similar to that which is the rule for the spindle-cells. Of the connected and individual character of those protoplasmic columns, I was able to satisfy myself in teased preparations. Part of one of these columns is represented in Fig. 29. From the position of the columns relative to the bundles of corneal tissue, the position and size of the nuclei, and from the absence of any other indication of spindle-cells, I infer that it is with spindle-cells we have here to do. But whether the condition of long protoplasmic columns is due to inflammatory change in the original spindle-cells, or whether we have before us a new formation—being part of a tissue destined to repair the injury which has been sustained—I am unable to say.

FIG. 29.—From inflamed cornea of a rabbit. Osmic acid. Red aniline. Dilute acetic acid. Magn. 400 diam.

The aniline dye, sold in England as *red aniline*, gives most instructive preparations of the spindle-cells when they have been previously fixed by osmic acid. The protoplasm of the cells is stained a deeper tinge than the surrounding tissues, and becomes prominently visible. If the section is stained very deeply in the aniline, and a drop of acetic acid is drawn by blotting paper through the glycerine in which it is mounted, and the effect watched under the microscope, the aniline colour is seen to disappear rapidly. There is a particular stage in this rapid bleaching process in which the contour of the spindle-cells is well marked in relation to the cornea substance in which they lie. At the same time, the contour of the nuclei is well seen. Permanent preparations of this kind are difficult to obtain, because it is not easy to control the bleaching effect of the acetic acid. Very beautiful preparations can be got by a double staining with red aniline and logwood.

The number of spindle-cells seen in such preparations varies according to the intensity and extent of the inflammatory process, and according to the extent to which the plane of the section happens to correspond to an inflamed tract.

The knowledge obtained by examining sealed serum preparations of the frog's cornea is thus confirmed by the osmic-acid preparations of the rabbit's cornea, and not only confirmed but extended.

The protoplasmic nature of the spindle-shaped body is made manifest by the granular, definitely-contoured substance, which is made prominent by the osmic acid. The nuclei are so well seen that the knowledge regarding them becomes exact. We find that the nucleus of each cell has divided into several distinct, small, rounded bodies, placed end to end. These readily stain by logwood and red aniline, whilst the normal undivided nucleus does not, from which it is to be inferred that the nuclei have not only divided, but have undergone a chemical change, by which their composition approaches that of the nuclei of the cells ordinarily seen in connective tissues, which are always readily stained by logwood.

When it is said that the nucleus divides, it is necessary to revert to the evidence obtainable regarding the condition of the nucleus in its normal condition. When these cells are demonstrated by gold solution being injected from the arterial system, the nucleus is usually seen as a single oblong body. Not unfrequently, however, the position of the nucleus is occupied by two oblong bodies, placed end to end—an appearance which seems

to indicate the condition in which a double nucleus exists in these cells. As four small nuclei are often observed in the inflamed cell, this would, in the case of a double nucleus, represent division of each of them into two parts.

In the healthy structure, the nucleus of the spindle-cells can be occasionally seen in a frog's cornea, examined in half-per-cent. salt solution, and it is then usually observed as a single oblong body.

We have thus obtained evidence that in an early stage of inflammation of the rabbit's cornea, before colourless blood-corpuseles are found in the sections (and when they are present, they can always be seen), the spindle-cells enlarge by an increase in the cellular protoplasm, and the nuclei divide.

In osmic-acid preparations of a rabbit's cornea which has been inflamed a week, we find at many parts of the cornea enlarged spindle-cells, similar to those I have just described as being seen in the earlier stage. But here we are able to compare them with the stellate cells and colourless blood-corpuscles. Their relation to the colourless blood-corpuscles will be better understood after I have described the latter. Their relation to the stellate cells is the following:—In a large proportion of the osmic-acid preparations, in which the spindle-cells and colourless blood-corpuscles are very conspicuous objects, nothing of the stellate cells is visible, whilst in a small proportion of such sections they become at once visible. In the very thin sections they can, however, usually be seen. In many sections in which they are not previously visible, they are seen after staining by the solution of red aniline, which is the method I recommend for their demonstration. In sections in which they are not previously visible, solution of extract of logwood and alum sometimes demonstrates them by a uniform staining of the cell substance; but it is somewhat difficult to manage this process, except in extremely thin sections, as the ground substance is apt to stain too deeply to allow the cell to become visible. The aniline staining is for this purpose much to be preferred.

The stellate cells and their fine processes are seen in most cases unaltered, even when they are surrounded by rows of swollen spindle-cells, and great numbers of colourless blood-corpuscles. In some parts, the globular form of the cell, and the beaded appearance of the processes previously described, are seen. Of the condition of the nucleus of the stellate cells in such preparations, little information is obtainable. When the osmic acid has acted alone, and no additional dye is used, the nucleus is invisible. When there

has been subsequent staining by logwood and aniline, the stained nucleus can be seen in the body of the cell, but not with sufficient distinctness to permit an accurate judgment regarding its condition. It is noteworthy, that in preparations in which the contour of the nuclei of the spindle-cells and white blood-corpuscles is indicated with the greatest precision by logwood and aniline, the nuclei of the stellate cells, although stained, are still obscure.

Fig. 30 represents the stellate, spindle, and colourless blood-cells in an osmic preparation of a seven days inflamed rabbit's cornea.

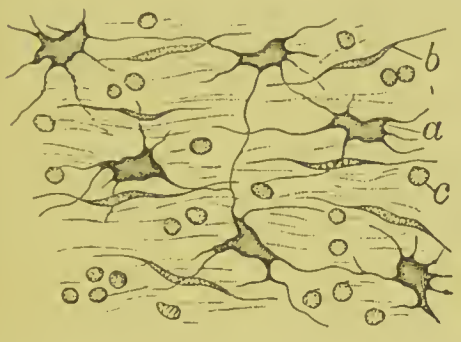

Fig. 30.—From a section of a rabbit's cornea seven days inflamed by thread. Osmic acid. Mag. 400 diam.
a, Stellate cells.
b, Spindle-cells.
c, Colourless blood-corpuscles.
(There being no further staining by logwood or aniline, the nuclei are not brought out.)

I have hitherto discussed the appearances of the spindle-cells as seen by methods which may be considered as comparatively perfect. There are other methods, in which the results are always imperfect, and have been consequently a fertile source of confusion and controversy. This is notably the case with gold preparations. If an inflamed cornea is placed in gold solution at that stage of the process in which the spindle-cells in osmic-acid preparations show granular protoplasm around and beyond the nucleus, and is then allowed to stain in acidulated water, there will frequently be seen in the cornea a number of oblong-shaped bodies arranged in parallel rows, and the rows in one plane frequently cross those above or below at a right angle.

Although these bodies are arranged in rows, they appear perfectly isolated from each other. They are further seen to be constituted by several small sharply-contoured, somewhat circular bodies, enclosed by a border of a very dark finely granular substance.

If the cornea or section is stained in logwood, the small central bodies are seen to be of the nature of nuclei, and to be arranged longitudinally in groups of two to four, corresponding in every respect with the spindle nuclei seen in osmic-acid preparations. Very frequently, nothing is seen but the nuclei, and they can be traced as following straight lines for considerable distances in the transverse planes of the corneal substance, the large undivided stellate nuclei being seen in the same tracts.

His first described this appearance, and it has since been seen and figured by many investigators. By His and others it has been ascribed to a proliferation of stellate cells; by Colnheim, Axel Key and Wallis, and others, to in-wandered colourless blood-corpuscles. They constitute the "spiessartige Figuren" and colourless corpuscles in "spindel-form" of these different authors.

It is unnecessary to point out the objections that can be taken to either view. The demonstration of spindle-cells in the normal cornea, which have, as regards their relation to the corneal substance and to each other, the same position which these much discussed elements have, and the results obtained by osmic acid in the inflamed cornea, show that they are the nuclei and protoplasm of the inflamed spindle-cells. The processes of the cells are by this method invisible, but exist none the less.

The *spiessartige Figuren*, and the colourless corpuscles in *spindel-form*, are the inflamed spindle-cells of the normal tissue.

When a tissue containing bloodvessels is treated by osmic acid, the red blood-corpuscles are stained and "fixed" in a very characteristic way, on which I need not enlarge here. Suffice it to remark, that in such preparations they can be diagnosed with great accuracy. In a cornea in which a subacute inflammation has existed for seven days or more, and in which new bloodvessels begin to be formed, there is in osmic-acid preparations an appearance to be observed in the spindle-cells of the area adjoining that of the formation of vessels which is of special interest. In some of the larger spindle-cells, sometimes covered by the granular protoplasm of the cell, and sometimes lying partly in and partly outside it, are small rounded or quadrangular bodies, which in point of form, evenness, and colour, exactly resemble the red corpuscles in the bloodvessels at other parts of the field. Most of them are smaller than the average red corpuscles. When such a section is stained in red aniline, the blood-corpuscles appear of a characteristic yellowish red tint, and the same peculiar tint is to be observed in the bodies seen in the enlarged spindle-cells. Nothing else in the preparation is similarly stained.

I shall return to this appearance when I come to treat of the formation of new bloodvessels in inflamed tissue. Meanwhile, I remark that I do not claim that the formation of red blood-corpuscles in inflamed spindle-cells is proven, but I do maintain that it is highly probable, and invites to further and more searching investigation. There are two obvious sources of fallacy, against

which I have been careful to guard. The spindle-cells of inflamed tissues sometimes undergo fatty degeneration, and in osmic-acid preparations of such tissues the cells are more or less filled with small globules of fat—seen stained as black spherical bodies, much smaller than the bodies in question, more perfectly spherical, and much darker in colour. These, again, sometimes coalesce to form large fat globules, considerably larger than a red blood-corpuscle. The nuclear products of spindle-cells, which are identical in appearance with red blood-corpuscles, are not so uniformly circular, are not so darkly stained, and are not so numerous as the fat globules sometimes seen in the same cells.

Since I first observed this appearance, I have not had opportunity of subjecting such sections to the chemical tests, which may throw additional light on the matter.

Another source of fallacy is the possibility of red blood-corpuscles having entered the cells from without. I have on rare occasions observed in an inflamed cornea, in which there were no bloodvessels, red blood-corpuscles, which I thought could only have come from the conjunctival vessels. But I do not think this could have been the case with the bodies in question. They were not only at some distance from vessels, but they were many of them smaller than the average red blood-corpuscles seen in vessels.

After the bundles of the corneal tissue have been separated from each other by serous effusion, and the spindle-cells have become enlarged, and so altered that they are easily visible, a greater or smaller number of colourless blood-corpuscles enter the cornea from the conjunctival border. The length of time that the inflammation has lasted before this takes place to an extent that can be considered abnormal, varies according to the animal, and the degree and extent of the inflammation. The only positive data I have as to the question of time, were noted in esculent frogs in winter, the inflammation being produced by solid nitrate of silver, and limited to a small point in the centre of the cornea. I found after twenty-four hours that although the spindle-cells were visible, and swollen in sealed serum preparations, very few colourless blood-corpuscles (or wandering cells) could be detected, but after forty-eight hours, in many of the "spaces" nearest the corneal border one or two corpuscles could be seen. After four days their number was much increased, and from two to six could often be counted in one "space," and they could be seen near the centre of the cornea.

I employ the term colourless blood-corpuscle as it is perhaps the one in most general use, but the term lymph-corpuscle, which is

also used, is probably a better one. "Leucocyte" and "white blood-corpuscle" are liable to the objection that the corpuscles are not white, and will both probably drop out of use. "Wandering cells," or shortly "wanderers," cells which Recklinghausen discovered in connective tissues, and which can be seen to possess the power of movement, have all the characters of colourless blood-corpuscles, and are, in fact, the same structures seen outside the bloodvessels in the lymph spaces of the tissues. Colourless blood-corpuscles, when they have lost their vitality, are seen as round granular bodies, and then constitute the structure which in pus receives the name of "pus cell." Set free on the surface of a mucous membrane either in a normal or pathological condition, the same colourless blood-corpuscle has been named a "mucous corpuscle." The sooner these various appellations are discarded in favour of a single one the better. They all refer to one and the same element, seen in various conditions.

To be able to tell what is and what is not a colourless blood-corpuscle in the inflamed cornea, is to be able to solve many difficulties, regarding which competent observers have formed very different opinions. Colourless corpuscles are liable to be mistaken for spindle-cells, and for nuclei of flat cells. I believe they can be distinguished by the following methods, which I have verified by examining portions of the frog's tongue, which I could see during the life of the animal to be crowded with colourless corpuscles which had escaped from the bloodvessels, the process of emigration having been observed under the microscope.

In the inflamed cornea colourless corpuscles can often be identified without difficulty when it is simply examined in aqueous humour, or better, examined after being one or two days sealed. But there are other appearances in such preparations, in regard to which it is very difficult to know whether they are colourless corpuscles or not. I believe that by this method it will be found difficult, if not impossible, to come to satisfactory conclusions regarding some of the changes which take place in the cellular elements.

In osmic acid we possess an agent which, in the present state of our knowledge, is indispensable in studying the colourless blood-corpuscles in the inflamed cornea. It fixes them in the form and size they possess in life. They appear mostly as round, finely granular bodies, the nuclei in which, without further staining, are not visible. When there are bloodvessels present, the colourless corpuscles present among the red corpuscles can be seen, and

form a criterion by which the identity of those outside the vessels can be established. About their identity, there can indeed be no doubt, as the action of osmic acid on colourless blood-corpuscles is the same in all tissues. By all other methods, the diagnosis between colourless corpuscles and spindle-cells is difficult; by osmic acid their confusion is impossible. The spindle-cells, in addition to their shape, are seen to possess the characteristic terminal processes. The cornea may be for many days crowded with colourless corpuscles, and none of them show any transition to that form and condition. Subsequent staining, first with logwood and then with red aniline, shows well the nuclei of the colourless corpuscles. In such preparations, they are seen in the cornea to contain two to four rounded nuclear bodies, stained a colour in which both the dyes are combined. These nuclei are grouped in circles. The nuclei of the spindle-cells are grouped in rows. In a preparation so stained, and in which there are many colourless corpuscles and swollen spindle-cells, they can be identified each as belonging to one or the other class, even under a very low magnifying power.

The question, Whether, in the new growth that follows inflammation, spindle-cells are formed by colourless corpuscles, is not prejudged by these remarks.

In osmic-acid preparations, the flat cells are invisible.

When the eye has become familiar with the differences between colourless blood-corpuscles and spindle-cells in osmic-acid preparations, it becomes possible to distinguish them in gold preparations.

The colourless corpuscles in a tissue which has been treated by half-per-cent. solution of chloride of gold, and subsequent exposure to light in acidulated water, are seen as perfectly circular bodies, even and homogeneous, having only about two-thirds of the diameter of the same structures when seen in aqueous humour or osmic-acid preparations. They are surrounded by a very narrow darkly stained uneven border, which from its constancy is probably part of the cell-substance. The nuclei are usually invisible as individual elements. The effect of the gold has been to weld the nuclei and cell-substance into a compact homogeneous body.

Inflamed corneæ, treated by gold, and subsequent exposure to light in weak acetic acid, can be preserved indefinitely in alcohol, and sections from such corneæ stained in logwood show the colourless corpuscles as round blue bodies. In sections of an osmic-acid cornea, nothing is seen of the "spaces," but in a gold-

stained cornea these can be seen, their position being indicated by the stellate nucleus. In a space there can frequently be observed lying beside the unmistakable large undivided nucleus of the stellate cell, one to three or four more deeply stained colourless corpuscles. These are most abundant near the border of the cornea. In the same preparations, the nuclei of the spindle-cells, generally divided, are also stained blue, being seen in groups of two or three, and recognised by the members of each group being placed end to end, and by the position of the groups being such that a straight line drawn through their longitudinal meridian would, if continued, cut them all into lateral halves. They are the visible divided nuclei of invisible chains of connected spindle-cells.

Inflamed rabbit corneæ stained in gold, and allowed to remain in weak acetic acid until their laminæ can be detached by the forceps, give preparations by which we learn how the colourless corpuscles enter the cornea. The laminæ, being sufficiently thin to be examined under the microscope, are stained in logwood, and the large nerve-trunks, if not otherwise visible, are then abundantly evident by the rows of stained nuclei. In a very successful preparation, the nuclei of the cellular sheath, which is continued on the nerve, are stained, as well as numerous nuclei on each medullated nerve-fibre. Between the cellular sheath of the nerve and the corneal substance by which it is surrounded, a perfectly colourless space can be made out, and in this space can be seen a varying number of stained colourless corpuscles. Sometimes they are seen in great numbers, and it can be observed that the "spaces" in the corneal tissue adjoining the nerve trunk contain them more plentifully than spaces which are more distant from it.

The same facts may easily be observed in the cornea of a rat The whole eyeball should be placed in gold solution for an hour, allowed to remain twenty-four hours in acidulated water, the epithelium then removed from the corneal surface, and finally, the cornea excised, stained, and examined entire.

The nerve-trunks are accompanied up to the corneal border by bloodvessels, and white corpuscles which leave the bloodvessels at that part are immediately external to the nerve, and have a free passage into the cornea along its outer border. They also enter the cornea from the ordinary lymph spaces of the sclerotic and conjunctiva, the spaces of these tissues being continuous with those of the cornea.

The forms which the colourless corpuscles assume in the inflamed cornea, may be separated into two classes, one in which identity of the structure is still evident; and another, in which ulterior organic changes take place, by which the appearance is so changed that the identity of structure may well be challenged. The latter series of changes will be described in a future chapter, when I shall treat of the structural changes which take place in inflammation. The former I will now briefly enumerate, premising that the description applies solely to osmic-acid preparations.

In a section of a cornea which has been inflamed until there are new vessels fully developed, it can be seen that the colourless corpuscles in the tissue are somewhat larger than those in the bloodvessels; and that of those free in the tissue some are larger than others. A great majority of the corpuscles are round; but sometimes, when they are in a layer, they have a hexagonal form, produced by mutual pressure. Others, lying singly, have forms more or less irregular, being club-shaped, or having rounded projections. Sometimes, on either side of a bloodvessel filled with red blood-corpuscles, they form a continuous column, as if they were contained in some tubular structure. They are more rarely seen in straight rows. When they are seen in this position, they touch each other, and are in numbers far too great to suggest that they can account for the spindle-shaped figures frequently seen in gold preparations; and which we have besides learnt to recognise in osmic-acid preparations as spindle-cells. The straight rows probably correspond to the longitudinal spaces between the primary bundles. They are thus seen in three different positions relative to the corneal structure—namely, as groups confined to the "spaces," in layers, and in rows. The first occurs earliest, the layers and rows being seen only after the inflammation is acute and has lasted for some time.

Sometimes a colourless corpuscle can be seen as a double body in osmic-acid preparations. Two rounded extremities, granular, and each about the size of a single corpuscle, are joined by a narrow band or isthmus. This connecting isthmus is not granular like the rounded extremities, being even and homogeneous in appearance. In logwood and aniline stained preparations, nuclei are seen in either extremity, but not in the isthmus.

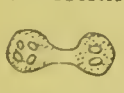

FIG. 31.—Colourless blood-corpuscle probably dividing into two. From inflamed cornea of rabbit. Osmic acid. Logwood. Red aniline. Mag. 150 diam.

In judging of the signification of these double corpuscles, it is necessary to bear in mind observations that have been made,

by Stricker, Klein, and Ranvier. In the inflamed tongue of the frog Stricker[1] saw the division of a colourless corpuscle into two in the living tissue. Klein[2] observed a similar division in the blood of the newt examined on the warm stage. Ranvier[3] observed the division in the blood of the axolotl, examined in the moist chamber, and gives a series of figures showing the stages of the division.

It is highly probable that the double corpuscle, seen in the osmic-acid sections, has been surprised by the reagent in the act of preparing to divide, and been "fixed" in the attitude.

As each of the rounded extremities of this double corpuscle is equal in size to the majority of the single corpuscles, it follows that the division is preceded by growth of the original cell.

In some osmic-acid sections, colourless blood-corpuscles are to be seen, which contain several nuclear bodies, which, judged by the tests formerly applied to similar appearances seen in some spindle-cells, are probably of the nature of red corpuscles. I have satisfied myself that these are not instances in which the red corpuscles have been taken into the substance of the colourless corpuscles from without, nor are they products of fatty degeneration of the cell. The relation which this fact has to the difficult problem of the genesis of the red blood-corpuscles is too important to be lightly passed over, but want of space prevents my entering on the subject more largely here. It may be, however, of interest in this connexion to call attention to an observation by Eichhorst.[4] He found, during five days, in the blood of a patient in the second week of typhoid fever, finely granular colourless cells, the diameter of which was four to six times that of colourless blood-corpuscles. These cells contained two to five, rarely seven, discs, which perfectly resembled the red blood-corpuscles, except that they were somewhat paler. By pressure, or the addition of water, they were set free from the mother cell.

Laptschinsky,[5] in studying the microscopic appearances of the blood in fevers, observed colourless corpuscles which contained nuclei deeply tinged with the colouring matter of the blood.

So much for what I believe can be ascertained regarding colourless blood-corpuscles in the inflamed cornea. If gold pre-

[1] Studien, etc., loc. cit.
[2] Centralblatt, 1870, p. 17.
[3] Archives de Physiologie, No. I., 1875.
[4] Deutsches Arch. f. Klin. Med., 1874, XIV. 223.
[5] Centralblatt, No. 42, 1874.

parations are controlled by osmie-aeid preparations, it will be seen that spindle-eells have often been eonfounded with them. For example, in Plate XVI., Fig. 7, illustrating Axel Key and Wallis's[1] paper on Keratitis, it is not diffieult, after an aequaintance with osmie-aeid preparations, to reeognise in the thiekly-set elongated eells, spindle-cells in which the eonnecting processes are invisible. But the authors' deseription is, that these are "spindle-shaped in-wandered eells arranged at right angles to eaeh other." The drawing is an aeeurate illustration of appearanees that are frequently seen in gold preparations, but more perfect methods show that the interpretation given to it is ineorreet.

In the next ehapter, I shall endeavour to eolleet into short compass what is known regarding the passage of the eolourless eorpuseles from the interior of the bloodvessels into the interstices of the neighbouring tissues, and sketeh the history of the discovery of this important aeeompaniment of inflammation.

[1] Virchow's Archiv, Band 55.

Chapter IV.

Extravasation of the Blood-Corpuscles.

I have in the two preceding chapters described the appearances which are to be observed in the cornea after it has been inflamed by irritants; and it has been shown that, although inflammatory changes take place in a non-vascular tissue, the intimate dependence of such an inflamed tissue on the nearest bloodvessels is soon demonstrated by the presence in it of the formed elements of the blood. The difference between a non-vascular tissue like the cornea, and the vascular connective tissue of other organs, is after all one of degree and not of kind. As regards its nutrition and also as regards the changes that take place in inflammation, the cornea is analogous to the islands of tissue, which are encircled by capillary bloodvessels, without being in actual contact with them.

The discovery that in inflammation the colourless corpuscles of the blood pass from the interior of the vessels into the surrounding tissues, and that they then constitute the formed elements seen in pus, and termed pus corpuscles, marks a new era in pathological science. The history of the discovery presents features of peculiar interest.

As early as 1843, Addison[1] maintained that the colourless corpuscles of the blood, mucous, and pus corpuscles, are identical structures, founding his belief upon their presenting the same optical characters and behaving similarily when brought in contact with different chemical agents. He further maintained that in the inflamed web of the frog's foot, the colourless corpuscles could be seen in the channels in which the red blood-corpuscles were visible, in the walls that bound these channels, and in the adjacent tissues. His views were not accepted by his contemporaries, who believed that the capillary vessels were closed tubes, out of which the corpuscles could not pass. Addison, not admitting that the capillary vessels were tubes with independent walls, found no such difficulty, and held firm to the facts which he satisfied him-

[1] Experimental and Practical Researches on Inflammation, etc.

self could be observed. His description is clear enough :—"The walls bounding the capillary currents become much more evident and more strongly defined in the inflamed vessels; they appear, however, to consist of parallel fibrinous fibres, which gradually amalgamate with the structure of the tissue, as they recede from the current of the blood; and it is among these fibrinous-looking fibres that the lymph globules are seen to accumulate."

To Addison must be assigned the merit of having first identified the colourless corpuscles lying free in the tissues with the similar corpuscles seen in the bloodvessels.

The belief then prevalent amongst physiologists, that cells such as those seen by Addison are formed *de novo* prevented his views being accepted.

In the *Philosophical Magazine* for 1846, Dr Augustus Waller, then a young medical practitioner in Kensington, published two papers, in the first of which he showed how the tongue of the frog can be made available for the study of the tissues in the living animal; and in the second, how in the inflamed tongue the colourless blood-corpuscles can be seen to penetrate the walls of the capillaries, and, passing into the tissues, there become "pus-globules."

Having secured the frog's tongue over a hole cut in a slip of sheet cork, and allowed it to be exposed to the air for two or three hours, he observed that over the "whole surface of the tongue there were numerous colourless corpuscles outside of the vessels, and occasionally a few scattered discs (red corpuscles). . . . In some instances, the manner in which the corpuscle escaped from the interior of the tube could be distinctly followed; that part of the tube in contact with the external side of the corpuscle gradually disappeared, and at nearly the same time might be seen the formation of a distinct line of demarcation between the inner segment of the corpuscle and the fluid parts of the blood in contact with it. Any slight agitation then was capable of disengaging the corpuscle from the vessel to which it was now external, and in its place a concave depression remained which appeared sufficiently protected by some membrane as to oppose effectually the exit of the discs and the fluid parts of the blood."

Stricker, in the Introduction to the *Studien*,[1] quotes the above passage and claims for Waller the priority of the discovery, but at the same time expresses the opinion that neither the text nor the figures in the plate which accompanied it were calculated to

[1] Loc. cit.

awake confidence. He rests this opinion on the fact, that Waller neither described nor figured a "neck" or pedicle in the corpuscle which was in the act of passing through the capillary wall.

I cannot agree with Stricker, in believing that the cause of Waller's great discovery being allowed to fall dead, was any omission in the description. Waller described appearances that were capable of verification, and he told his readers how to verify them. All that was required was a frog, a sheet of cork, a microscope, and a moderate amount of patience. The problem to be solved was of importance enough, it might be supposed, to have overcome the natural suspicion with which statements of new facts are always regarded, and to have provoked a repetition of Waller's experiment. But this does not seem to have been the case. I can find no evidence that any of the distinguished physiologists contemporary with Waller thought it necessary to follow his simple directions, or to take any notice of his papers whatever. Had they done so, the "neck" of the corpuscle would have been observed in due time. As it was, one of the few great discoveries that have marked a turning point in the history of medicine—and not the least of them—was locked up in the pages of the *Philosophical Magazine* for twenty years.

It was believed at that time by the best authorities that "pus cells" are formed in a blastema; and so impregnable was this theory, that Waller's description of how their true origin might be seen was disregarded on account of its inherent improbability. It is curious to note that although the faith in the blastema theory was too strong for a demonstrable truth, it could not resist another hypothesis, the "proliferation of the connective-tissue corpuscles," which the genius of Virchow imposed unconditionally on Europe, and which was received for twenty years with scarcely a protesting voice.

Augustus Waller, the first observer of the emigration of the colourless corpuscles of the blood in inflamed tissues, after a life spent in alternate intervals of medical practice and physiological investigation, finally settled at Geneva in 1868, and died there in 1870.

Cohnheim, who knew nothing of Waller's papers, again discovered the emigration of the colourless corpuscles in the inflamed mesentery of the frog, and published his discovery in *Virchow's Archiv* in 1867. Thanks to the high scientific reputation of the author, and the medium through which his essay was communicated to the scientific world, it at once attracted the attention of pathologists. His experiments were immediately repeated; and

although some observers were not able at first to follow all the details of the process as he described them, the accuracy of his observations has within the last few years been abundantly attested.

Experiments of the kind had in the meanwhile been much facilitated by Stricker's discovery, that diapedesis of the red corpuscles can be observed in frogs which are under the influence of curari.

When inflammation is produced in a vascular organ, there are certain phenomena which are always present, and which must therefore be considered as essential parts of the inflammatory process. An account of these, as they are seen in a transparent tissue, will serve as a typical description; and in the interest of the reader, I will, although conscious of my inability to do justice to the original text, translate Cohnheim's description of the appearances observable in the inflamed frog's tongue. I quote from a work he has lately published.[1] "When a small piece of nitrate of silver is placed on the surface of the tongue, slight muscular twitchings generally appear in the neighbourhood of the caustic, a rapid dilatation takes place first in the arteries which supply the cauterized spot, and then in the veins which have their origin in it. All the capillaries of this part are filled with blood in the most striking way. The hyperæmia extends not only to the vessels whose branches are directly acted on by the caustic, but also (especially if a somewhat large piece has been used) always to other vessels in the neighbourhood, so that the hyperæmic zone may attain very considerable dimensions. As long as the dilatation is increasing, and for some time longer, the blood flows in the whole of the widened vessels with great rapidity; and it is an exceedingly striking thing to compare the vessels of the hyperæmic zone with those which have not undergone dilatation, and in which, therefore, the blood flows at the original rate of speed. But the scene soon changes. First in the vessels whose terminal branches are directly in the cauterized spot, there are effects visible which show that in these branches the circulation is arrested. It is exactly as if the vessels, as far as the caustic directly reaches and acts, were tied, and rendered impermeable. In the arterial branch which leads directly to the cauterized part, the onward movement, after several futile and fitful efforts to drive the blood-column forward, comes to an end, and the blood in it stagnates; on the other side, in the venous branches which arise from the cauterized part, the movement becomes gradually slower and slower, until

[1] Neue Untersuchungen über die Entzündung. Berlin, 1873.

there also it comes to a standstill,—stagnation. In both arteries and veins, the stagnation extends to the first collateral branches which lead to and arise in parts beyond the cauterized spot. In these parts the circulation is still rapid, and all the more so in the arterial collateral branches, on account of the increased tension produced by the occlusion of the affected artery. In the veins, the arrest of the circulation in several of the radicles leads of course to the circulation being slower; nevertheless, even when the still open collateral radicles do not directly correspond to the collateral arteries, the general acceleration is usually at first so great, that in veins at whose origin stasis has taken place, the blood circulates more quickly than it did originally before the cauterization. Of course, there is stasis in a number of the capillaries, not only in all those which have been directly affected by the caustic, but also in some of those immediately adjoining, as far as they form the connecting channels between the stagnant arteries and veins. All these are the evident—so to say, the mechanical—effects of the caustic, and they exhibit manifold modifications according as a larger artery, or a vein of greater calibre, happens to have been affected. These modifications may be left without further consideration, as their varying features may be easily deduced theoretically, and as I have treated of them at large in previous publications.[1]

"To these changes in the condition of the vessels of the hyperæmic zone—which are of purely mechanical origin—are added, sooner or later, others which are not less striking. In about one or two hours after the application of the caustic, first the dilated arteries which are furthest removed from the cauterized part begin to contract, and therewith the circulation in them becomes slower. This is naturally followed by slower circulation in the corresponding veins, and the more so, as it is much longer before their dilated condition begins to diminish. The vessels which are nearer follow the more distant ones in this respect, until, after a few hours, in most of the previously dilated arteries, and a little later in all the corresponding veins, the lumen and the rate of circulation have returned to the normal condition. Only those vessels, arterial and venous, which lead directly into the cauterized part remain permanently dilated over a shorter or longer part of their course, and especially the veins, whose lumen remains permanently twice or three times the diameter of the veins which arise at a distance

[1] Venöse Stauung. Virchow's Arch., Band 41, p. 220; and Embol. Processe, Absch. I.

from the eschar, but which were originally of the same calibre as those affected by the caustic. The dilatation of the affected arteries is also usually considerable; yet the relation of the diameter between the respective arteries and veins, in accordance with which that of the latter is much the greater, is preserved. But even these vessels, although they have contracted so little, no longer present the same spectacle as formerly shortly after the application of the caustic. For, in spite of the dilatation, the circulation has become gradually slower in them, and not only in the veins, in which, in about five or six hours after the cauterization, the blood creeps along with a very lazy movement, but also in the arteries, in which there is no difficulty in distinguishing the individual corpuscles. This slow circulation extends often to the neighbouring branches, which had been for a considerable time the scene of a collateral accelerated circulation. The latter condition now shows itself in one or more of the still more distantly situated lateral branches.

"Whilst the condition of the arteries and veins in the vicinity of the cauterized part is such as has been described above, not less striking changes take place in that of the capillaries. Those more distant from the eschar have gradually, under the influence of the progressive contraction of the arteries, got quit of the excessive quantity of blood by which they were distended, and again present their original appearance of small channels, in which a light yellow stream flows with moderate rapidity, and in which the formed elements can be mostly recognised without difficulty. On the other hand, in the part immediately surrounding the eschar, the stasis in some of the capillaries remains complete; now, as formerly, are to be seen capillaries in which the contents have been moulded into an apparently homogeneous mass, whose colour is of a carmine to a bluish red, and in which there is naturally no visible trace of movement. The only difference, compared with their condition when stasis was beginning, is, that these small vessels seem wider. But what is much more striking is, that the number of stagnating capillaries has become larger; not only those which lie close on the eschar, but also a second and third zone, and even more, have passed into complete stasis, and in them also there is the same absolutely motionless homogeneous red mass. Further outwards from these stagnating capillaries, comes a broader or narrower zone, in which they are still more filled with blood than they originally were, and in which movement is still undoubtedly present, but is exceedingly slow; and it is only beyond these that we come on

capillaries which, in their condition, can in no way be distinguished from those of the rest of the tongue. The picture which, as a whole, that region of the tongue presents, which some time previously has been cauterized with nitrate of silver, may be summarily described thus:—

"In the immediate vicinity of the eschar, which has in the meanwhile become black, there is a somewhat broad zone of complete stagnation in all the vessels; further, the arteries and veins which lead directly into the eschar are dilated over a greater or less extent, and the blood flows through them slowly; finally, a similar slow circulation and distension with blood is seen in a circular zone of capillaries which bounds the periphery of the region of perfect stasis; everywhere else in the tongue the vessels present absolutely their usual condition. In most cases this is the picture which can be seen six or eight hours after the application of the caustic; but I have, in the above description, intentionally abstained from giving any fixed data in figures, either as regards the duration of the separate stages or the relative calibres of the vessels, because the greater the number of frogs (rana esc.) on which I studied these appearances became, the more was I convinced that, in this respect, there are very great differences. Whilst, in one animal, the stage last described is reached in two to three hours, ten or twelve elapse before it is reached in another. As might have been *a priori* expected, the whole proceeds quicker in summer-frogs than in winter-frogs; but that is the only difference between them.

"In the course of the next six or eight hours a new set of phenomena are to be observed in the vessels. First, there is often still a good deal of dilatation, especially in the arteries, less striking, although quite evident, in the veins, which are situated near the cauterized part, without, however, touching it; a condition that, in the rich supply of vessels to the tongue, must often be the case. But what is most interesting in these dilatations is, that they are usually quite limited, being entirely restricted to that part of the vessel which is adjacent to the eschar; whilst beyond this part, in both directions, the same vessels are of the usual width. In the sections of localized dilatation, the circulation is naturally very slow; and, of course, most so when it occurs, as is often the case, in one of the lateral branches of the artery which leads to the cauterized part, in which, as follows from the explanation given above, the stream is in any case slow. Secondly, there commences at this time, with very small beginnings at first, a

process which henceforth will more than all else engage our attention, namely, extravasation. Generally it is some of the capillaries in the zone of slow movement, but sometimes one of the dilated veins, whose contour is first rendered uneven by extravasating blood-corpuscles; if it is a vein, then it is always colourless corpuscles, which, as I may remark in passing, accumulate regularly on the inner coat of all the veins at the time the circulation becomes slow, and remain permanently in this position; from the capillaries, on the other hand, both coloured and colourless corpuscles pass out from the beginning. The process, which takes place to a slight degree at first and at isolated points, becomes gradually more and more general. The veins are surrounded by colourless corpuscles, which soon embrace them several rows deep, and not the less increases more and more the passage outwards of the blood-corpuscles from the capillaries. At first it may have been only the capillaries of the zone of slower circulation from which the extravasation took place; but after some time those of the external stasis-zone take part in the process. But here the diapedesis of the red corpuscles is greatly in excess. The capillaries become bordered with even thicker masses of them, so that they to a great extent fill the intermediate spaces between the adjoining bloodvessels. This does not extend to the inner stasis-zone; here the contour of the distended capillaries remains quite even;—not a single corpuscle is being extravasated. On the other hand, in the course of the next and the following days, the process extends further peripherally, and that in two ways. The belt of distended capillaries through which the blood has been hitherto slowly moving, now passes into more or less complete stasis, and becomes conspicuously the seat of an ever-increasing diapedesis; but further, the next zone, which has been hitherto free, begins to be affected, and the capillaries become fuller, the blood flows through them more slowly, and there is an emigration from them of white and red corpuscles. The breadth of this last zone may be somewhat extensive. Meanwhile the emigration from the affected veins continues, and in the smaller veins, a few red corpuscles pass out with the white, which constitute by far the greatest proportion; only the contour of the arteries remains perfectly even. At the points of localized dilatation, where the circulation is very slow, and where mostly the arrangement of the white corpuscles along the inner wall of the vessel is exceedingly marked, not a single corpuscle leaves the channel; contrasting so much the more with the localized dilata-

tion of the veins, where an abundant contingent is given to the extravasation. Accordingly, on the second, third, and fourth day after the cauterization the appearances are the following:—Around the eschar a small zone of absolute stasis, then a relatively broad zone of stagnating capillaries, from which an enormous number of red corpuscles pass outwards, then a still broader zone of capillaries with a slow circulation, from which the most abundant extravasation of coloured and colourless corpuscles takes place; at the same time considerable extravasation from the dilated veins in the neighbourhood of the eschar, in which the blood is moving slowly. At some distance from the part everything is normal. The capillaries adjoining the zone of extravasation are fuller than is the case in the ordinary conditions; but of extravasation of red or colourless corpuscles nothing is to be observed, and still less in the capillaries further removed, in which the contents and current are normal. But the extravasation from the veins is limited to the vicinity of the cauterized part; at some distance there is nothing of it to be seen, let the current be ever so slow, the dilatation ever so considerable. In the veins which take their origin directly in the cauterized spot this remarkable condition is often enough observable; as has been already described, they are regularly dilated and the blood flows in them with great slowness until the point where they receive another branch, the circulation in which, being normal, produces more active movement in the venous trunk. Invariably, as far as the slow circulation extends, there is the most typical accumulation of colourless corpuscles on the inner vascular wall, but extravasation is seen only in the vicinity of the eschar; it ceases completely at some distance from it. Thus the eschar is now surrounded by a crowded mass of red and colourless blood-corpuscles, the former, on account of their colour, being naturally the more conspicuous, but by careful observation the colourless cells can be recognised everywhere amongst the red ones, and in the peripheral zones they outnumber by far the coloured ones; on the other hand, the former are often seen close to the eschar, in the area of complete stasis, whither they have in such cases wandered from without. There is, further, at this time, always a great number of colourless corpuscles in the corresponding lymph-spaces of the tongue, especially in the principal sinus which is situated in the posterior attached portion. But that it is not only the formed elements of the blood which have found their way from the circumference of the eschar into the lymph-spaces of tongue, is shown by the considerable and often

tense fulness of the lymph-sacks with watery fluid. This comes from the vessels round the eschar, being a product of the active transudation which has accompanied the extravasation of the corpuscles of the blood. To this is also to be referred the fact, that the eschar projects above the level of the rest of the tongue. This is always the case, and often to a considerable extent, when the cauterization has not affected the whole thickness. If it has done so, only the borders of the eschar are elevated, the centre constituting a pit-shaped depression. Everything remains for a series of days in the condition described; but extravasation and transudation finally cease, the lymph-sinus at the root of the tongue collapses, the colourless cells gradually disappear from the circumference of the eschar, whilst the red ones remaining form the bloody circle which is long seen around it; but weeks usually elapse before the black eschar is completely loosened and removed."

The principal features in this account of the changes which constitute inflammation are divisible into two categories. The first in order of time consists in dilatation of the arteries and veins, consequent distension and rapid circulation in all the vessels of the part, and accumulation of colourless corpuscles on the inner wall of the veins.[1]

Colnheim has proved by a series of experiments, that it is possible to produce these effects without the process proceeding further, the circulation gradually becoming normal, not a single corpuscle having left the vessels; up to this point he does not believe that the term inflammation is applicable. But when these changes have been produced by the application of a caustic, they are followed by a second series, of which permanent dilation of the artery and vein leading to the cauterized spot, a progressive stasis in the capillaries, and extravasation of blood corpuscles are the chief. These facts have received explanation on several hypotheses. That given by Colnheim I quote in his own words. "By

[1] A momentary contraction of the arteries has been observed by Mr Lister and others to follow immediately the application of some irritants. It gives place in a few seconds to dilatation, and it is evidently not an essential link in the chain of phenomena. I do not enter on the question of the mechanism by which the muscular fibres of the arteries suddenly relax, because I do not feel warranted in discussing an unsettled and difficult physiological problem, to the solution of which I have nothing to contribute. The view which considers it as being nothing more than paralysis of the muscular coat of the arteries, and probably also of the veins, as the direct effect of a local cause, seems to me, however, in the absence of direct proof to the contrary, the more probable one.

the application of the caustic, a sudden injury to the vessels and disturbance of the circulation of the nutritive fluid in the tissues is produced, the result of which is a dilatation of the vessels of the part without the co-operation of any reflex action. The accelerated circulation which necessarily accompanies the dilatation begins after a time to slacken, first in the arteries, later in the veins, so that the effects which follow the application gradually subside. Then there begin slowly, and step by step, the changes which are produced on the vessels next the eschar by the direct action of the caustic and of the chemical products of which it has been the cause. These gradually extend outwards, but always so that the vessels nearest the eschar are most, and those further removed least affected." Cohnheim believes that the sole cause of the stagnation and the extravasation is to be found in an abnormal condition of the walls of the vessels directly produced by the caustic. He has shown by experiments on the nictitating membrane of the frog and the rabbit's ear, that stasis and extravasation can be observed without the preliminary dilatation of the vessels, if care is taken to apply the caustic, so that no vessel is directly touched by it. He considers that he has eliminated the possibility of reflex action by showing that the phenomena take place in the same order in the frog's tongue when all connexion between the tongue and the animal has been severed, except the lingual artery and vein. With reference to the exception that might be taken to this experiment, namely, that a reflex action may be possible through the medium of the vaso-motor nerves, he points out that no ganglia have been shown to exist on these nerves.

Mr Lister has shown, many years ago,[1] by a series of simple and well-devised experiments, that at least one cause of the tendency of the corpuscles in the blood which flows through an inflamed part to adhere to each other, and to the walls of the vessels, is connected with changes in the vascular wall, the vessels becoming so altered, that they act like a foreign body on the blood which is in contact with them. To illustrate the nature of the experiments by which this was shown, I quote part of the account given of one of them. "In a case," he remarks, "in which the circulation was perfectly natural in the web, and the corpuscles moving on at slight intervals, with no tendency to adhere, on a drop of chloroform being applied, I saw the very same corpuscles instantly become checked in their progress by sticking to each other and to the capillary walls, and move on

[1] Phil. Transactions, 1858.

slowly in masses, with considerable intervals. . . . That the effect on the blood within the vessels of a part inflamed by chloroform is secondary to a change in the tissues, is further proved by the circumstance that abnormal accumulation of slowly-moving corpuscles may last for hours together without stagnation, as a consequence of the application of this irritant for an extremely brief period. Long after all the blood which could possibly have been directly acted on by the chloroform has left the vessels, successive fresh portions continue to experience precisely similar changes in passing through the irritated area."

That the adhesiveness of the colourless corpuscles is not the only cause of their attaching themselves to the wall of the vessel has been shown by Cohnheim, who found that when the blood current was shut off by temporary occlusion of the main artery, the corpuscles left the wall of the vessel and mixed with the others in the centre of the vessel, but that when the current was re-established they again adhered to the wall.

Arnold has described minutely appearances presented by the colourless corpuscles, which indicate that they are acted on by the stream of serum which passes outwards through the weakened wall of the vessel, and assigns to this action an important part in the phenomena of adhesion and emigration.

As soon as the fact of the extravasation of the blood-corpuscles was established, the problem that presented itself for solution was how to account for the passage of solid bodies through an apparently unlacerated tube. The question received various answers, to which it is not necessary to refer, as the investigations of Professor Arnold and Dr Laidlaw Purves, carried on independently of each other, have solved the chief difficulty. The epithelium that constitutes the inner surface of the capillaries and smaller veins was first demonstrated by the injection into the vessels of a solution of nitrate of silver mixed with gelatine. After exposure to the light the outlines of the cells were seen as irregular black lines. By a similar procedure the points of exit of the corpuscles were determined. An animal in which the extravasation was going on was killed, and the vessels injected with silver solution. The colourless corpuscles were found fixed in the wall of the vessel, and it was then evident that they passed outwards between the epithelial cells. They were fixed in the dark lines that indicate the cell contours.

When epithelial membranes are treated by silver, a dark mass is often seen at the angles of junction of the cells. Great im-

portance has been assigned by Arnold to such masses of albuminate of silver when seen in inflamed capillaries, and he describes them minutely, the smaller as stigmata and the larger as stomata. Exudation is supposed to take place freely at these pores; but the extravasation of the corpuscles is not limited to these points. Dr Purves describes the emigration as taking place "not seldom where three cells meet, but more often between two cells, and especially in the neighbourhood of the end of the cell."

The œdema that takes place so rapidly in inflammation, shows that there is an abundant passage of the fluid elements of the blood through the vascular wall, and the observations of Arnold show that this takes place chiefly, if not entirely, through the same interepithelial spaces in which the corpuscles can be seen. He infers this from observing the passive movements of corpuscles which are in the act of passing through. These justify the inference that there is a stream which passes through with the corpuscle, and carries it away from the point of exit.

That the vascular wall has, as a direct result of the inflammation, undergone a change by which it offers less resistance to the pressure of the blood, has been proved experimentally by Winiwarter.[1] He found that in the frog injection masses were extravasated from the vessels of the mesentery by a much weaker pressure when the mesentery had been inflamed than when it was healthy.

I have previously shown, that when a part of the cornea is cauterized the resulting change in the tissue can often be traced in a localized tract which stretches towards the conjunctival border. There the affected tissue is in direct contact with the walls of the bloodvessels, which in their turn suffer from the injurious influences which originate in the wounded part. As soon as the vessels have been reached, the usual phenomena of inflammation present themselves, and many of the extravasated colourless corpuscles find their way, as we have seen, into the corneal tissue.

The direct result of the inflammatory process, whether in a vascular or non-vascular tissue, is thus to fill the interstices of the inflamed part with the formed and unformed elements of the blood. These exuded elements provide the means of repair to the damaged tissues. The changes by which this is accomplished will be discussed in the next chapter.

[1] Der Widerstand der Gefässwände im normalen Zustande und während der Entzündung. Wien. Akad. Sitzb. lxviii. 1873.

CHAPTER V.

Two papers by Mr Lister, in the *Philosophical Transactions* for 1858, "On the Cutaneous Pigmentary System of the Frog," and "On the Early Stages of Inflammation," introduced to the notice of pathologists a new field for the study of inflammatory change. Nothing of much moment has been added to Mr Lister's observations, and although the line of research indicated by that author remains one of the most promising, it has been comparatively neglected. This may at first sight seem strange, as the examination of the pigment in the web of the frog's foot is simple enough, but I believe it is to be accounted for by the fact that there underlies this subject one of the most difficult and, vital points in histology.

When the web of a frog's foot is examined under the microscope, it is found to contain numerous masses of black pigment. The pigment may be concentrated in isolated circular dots, or form an unbroken network. In the former condition, the skin when looked at by the naked eye appears pale, in the latter dark. Between the concentrated and diffused conditions all possible intermediate stages can be observed. In, or on, the edge of the central mass of pigment a large oval nucleus is frequently to be seen. Hence these bodies have been believed to be cellular, and have been known as pigment or chromatophorous cells. When they passed from the diffused or intermediate stellate form to that of round isolated bodies, this was (and is I suppose still by most authorities) regarded as being produced by a retraction of cell processes, and when they again became diffused, the processes were believed to project until they met and ran together. Here, it was natural to suppose, is an excellent opportunity of studying the changes that take place in cells under different influences. But Mr Lister came to another conclusion regarding these appearances. He found (*loc. cit.*, p. 680) that "the Germans had taken an entirely erroneous view of the phenomenon, attributing the round form of the masses of pigment to contraction of the branching offsets of stellate cells, whereas it turned out that the

chromatophorous cells do not alter in form, but that the colourless fluid and dark molecules which constitute their contents are capable of remarkable variations in relative distribution, the molecules being sometimes all congregated in the central parts of the cells, the offsets containing merely invisible fluid, while at other times the colouring particles are diffused throughout their complicated and delicate branches; and between these extremes any intermediate condition may be assumed. It further appeared that concentration of pigment takes place in obedience to nervous influence, while diffusion, though also an active vital process, tends to occur when the pigment cells are liberated from the action of the nerves." Mr Lister found that the action of irritating substances "paralyzed" the pigment "cells," and that so long as the effect of their application remained, although the pigment in the cells in the neighbourhood of the affected part was capable of changing its condition, that which was within the area of the substance applied remained fixed in the original position. It is impossible for me, in the short space at my disposal, to attempt to give even an outline of Mr Lister's experiments. The papers referred to should be read by all who are interested in the study of inflammation.

When I first began to observe the changes in the pigment bodies, I adopted Mr Lister's views regarding their nature, and in the abstract of a paper on inflammation, published in the *Proceedings of the Royal Society*, No. 160, 1875, I compared certain appearances observed in the stellate cells of the cornea to a "collection of the protoplasmic particles in the centre of the cell, similar to that which takes place in concentration of pigment." In the second chapter of the papers published in this Journal, whilst describing the spherical condition observed in the stellate cells of the cornea, I did not give expression to the hypothesis of the concentration of protoplasmic particles, which may or may not be true, and in any case is not proven, and I purposely delayed all reference to the pigment cells, hoping that before these papers were brought to a close an investigation into the nature of these bodies, with which I was from time to time engaged, would be so far advanced that I should be able to express a definite opinion as to their structure. The investigation is still incomplete, but as this is the last chapter I shall write on the subject at present, and as the question is intimately connected with that of inflammation, I cannot pass it over in silence, more especially as my further researches connected with it may be indefinitely delayed.

I have come to the conclusion that these pigment bodies are neither cellular, as usually maintained, nor masses of pigment granules suspended in the fluid contents of cells, as is believed by Mr Lister. Without burdening the reader with a mass of technical details, I may mention that the methods on the results of which I base this view consist chiefly in submitting small portions of the web to a process of digestion, by placing them in the stomach of a newly killed frog, and in treating portions of the web and other parts of the skin by saturated solution of caustic potash, according to the method minutely described by me in the *Quarterly Journal of Microscopical Science* for January 1876. By these methods I succeed in isolating portions of the pigment in small patches and in a complete network. When isolated from the tissue they never contain a nucleus. On the other hand, in partially digested skin the large nucleus is left behind, and is seen to have a fixed and firm relation to the tissue, whilst the pigment has none, either to the nucleus or the tissue. To complete the investigation it is necessary to discover the nature of the cell whose large nucleus is visible amongst the pigment.

I believe that the pigment is contained in the interstices of the tissues, but that at the same time it is in certain parts capable of penetrating the substance of cells, as for example in the choroid. This view, so far from diminishing the interest of Mr Lister's experiments, increases it; for in observing the movements of pigment, we observe some of the changes that take place in the contents of the lymph spaces, a series of changes of which we as yet know almost nothing. In diffusion of pigment we have, as I believe, a natural injection of those intermembranous interstices which Recklinghausen has described as *Saft-kanälchen*. The mechanism by which the pigment accumulates in the dilated central points of these interstices is unknown.

For the sake of completeness I must here further interpolate by adding a few remarks on "giant cells." Any granular ill-defined mass containing in its substance a number of nuclei or nuclear vacuoles, is termed a "giant cell." Such masses are found constantly in the marrow of young bones, in certain tumours of the lower jaw, and in tubercular deposits. They are further found in granulations of wounds however produced (Jacobson), in chronic ulcers (Brodowsky), in typhoid ulcers (Klein), and according to Jacobson they have been described as existing in tumours, glandular swellings, elephantiasis, lupus, syphilitic gummata, abscess of the mamma, etc. To regard these structures as having a specific

relation to any particular disease, as has been done for tuberculosis, is unjustifiable. Axel Key and Wallis observed in the inflamed cornea large cells with twenty nuclei which correspond to the definition usually given of a "giant cell." I have never seen such a cell in the inflamed cornea, but I have on several occasions observed in serum preparations masses of conglomerated colourless blood-corpuscles, in which the outlines of each individual corpuscle were so faint that at first I was inclined to consider them as single many-nucleated structures. More careful examination showed that they were without doubt colourless corpuscles. In osmic-acid preparations this difficulty never occurs.

I have described, in a paper on the Structure of Cartilage (*Quarterly Journal of Microscopical Science*, January 1876), a preparation in which a transverse section of healthy articular cartilage, after being sealed in blood serum for seven months, was resolved into an immense number of the structures designated giant cells. A most interesting series of experiments by Ziegler[1] throw much light on this question. This experimenter fastened two small squares of glass together so that a very narrow space was left between them, and inserted them in the subcutaneous tissue of a dog. The wound closed over the squares, which were dissected out after various intervals of time, treated by osmic acid, and examined under the microscope. The space between the squares was partly occupied by colourless blood-corpuscles in all stages towards fully developed "epithelioid" cells, and by giant cells. So much for the fact observed. Ziegler's theory is that the giant cells are formed from the colourless cells by the development of one cell, which consumes its neighbours, and grows at their expense. The nuclei of the giant cell are not the nuclei of the colourless corpuscles, but nuclei formed by division in the growing "giant cells." This process of consumption and growth is purely hypothetical. Not a single fact is brought forward to support it, and the drawings afford proof that no evidence has been attainable. What Ziegler has shown is, that between his glass plates colourless blood-cells develop into epithelial (or epithelioid) cells, and that later the shapeless masses known as giant cells are also seen. I believe that in Ziegler's experiments, after the epithelium had been formed, it lost its vitality and degenerated into an ill-defined cell-conglomeration. I cannot dwell on the subject, but will take the liberty of stating my belief dogmatically, that "giant cells" are either the product of disintegration of layers of flat cells in tissues undergoing

[1] Experimentelle Untersuchungen, etc., von Dr Ernst Ziegler. Würzburg: 1875.

absorption physiologically or pathologically, or are produced by an abortive effort on the part of colourless blood-cells to form such a layer. In disintegrating processes their form will depend to a certain extent on the tissue in which disorganization is taking place, and a "giant cell" may, amongst other things, be simply a dead and disintegrating capillary vessel. In all inflammatory processes the occurrence of "giant cells" is possible, and is in no sense specific.

When the destructive effects of the inflammatory processes have ceased, the elements which have lost their vitality undergo various changes, and are either discharged from a free surface or are absorbed, and a new tissue is formed which is destined to restore the lost integrity of the part. Every step of this process is as much a matter of controversy as are the primary inflammatory changes discussed in the earlier chapters of these papers. In this instance, however, considerations of space prevent my entering minutely into the histological details, and I shall, instead of criticizing the various doctrines which are taught by pathologists, give a summary of my own views, and the nature of the investigations on which they are founded.

The plasma which escapes from the bloodvessels of an inflamed part coagulates, as is very strikingly shown in pericarditis or pleuritis, when the surfaces of the membranes are covered with the soft yellowish substance, which at a later period is capable of becoming organized and forming false membranes. This substance is coagulated blood plasma, and contains a greater or less number of colourless blood-corpuscles. From these two elements—the formed and unformed, or cellular and non-cellular—the newly formed tissue takes its origin.

The blood plasma contains albumen and fibrine-forming substances, whilst the fibrillary tissue that forms the groundwork of the new growth is largely gelatinous. The mechanism of the formation of this gelatinous tissue is not understood. What can be observed is, that in a transparent homogeneous substance, rich in cells, fibrillation takes place, and with this fibrillation the tissue begins to assume its characteristic and permanent appearance. If accurate knowledge has not been obtained regarding this process, theory has as usual done its best to make the want unfelt. The theories regarding the question are not many, and have their source in the opinions which have long held undisputed sway regarding certain imaginary properties of cells. Some observers describe the fibrillæ of the gelatinous tissue as being given off

(I may say shed) by spindle cells. These cells, according to this view, manufacture the tissue out of their own substance, which is renewed by a process of nutrition as fast as it gives off the new tissue. Others attribute the fibrillation to an influence exerted by the cells on the amorphous material around them. Others again believe that the tissue is formed by lymph cells which become transformed into the new substance. None of these theories have passed from the region of hypothesis into that of fact. They are unproved.

I may illustrate the insecurity of the foundations on which prevailing doctrines regarding the growth of tissues rest, by referring to Max Schultze's theory of the formative activity of the cell, and the kind of evidence which has been considered satisfactory in histological questions. Schultze, observing that in embryonic muscle cells are prominent objects, and that in fully-formed muscle, nuclei are to be found in the substance of the muscular fibre, and around the nuclei a scant amount of granular substance, came to the conclusion that the large volume of muscle substance is a product of the cell, the nucleus and a small amount of the cellular protoplasm persisting. The amount of muscle substance formed being out of proportion to the number of nuclei observed, he framed the theory of the formative activity of the cell. Mr Fitzjames Stephen, in his book on Liberty, Equality, and Fraternity, accounts for the complacency with which erroneous doctrines are accepted in ethical science, by a passion in human nature to theorize, and to cling with faithful devotion to any theory which gratifies the love of order inherent in the mind. Some such love of order has prompted the readiness with which Schultze's theory has been embraced by histologists. Dr Beale had previously announced a theory which was perfectly identical, but unfortunately condescended to give a reason. Max Schultze's arguments were simply statements of belief, and criticism was disarmed. Dr Beale disturbed the composure of unreasoning faith by his carmine. Schultze's cell is Beale's "germinal matter," the muscle substance produced by the formative activity of the cell is the "formed matter." What is stained by carmine, forms; what does not stain, is formed. Even its simplicity could not secure acceptance of such a reason. Schultze, as it seems to me, has been awarded too exclusively whatever merit may belong to the theory, which, to say the least of it, is as much Beale's as Schultze's. Neither of these able histologists adduced a single observation in support of it, and it might just as well have been imagined by a

poet as by a histologist. In a paper published in this Journal, to which I have several times had occasion to refer (September 1874), I tried to show that the nuclei of muscle are the nuclei of cells that can be observed in and isolated from the muscle substance. For more complete evidence of the same fact, I refer to a paper on the histology of muscle, published in the current number of the *Quarterly Journal of Microscopical Science*. All that Schultze was warranted in affirming was, that there are nuclei in a muscular fibre. I am now warranted in stating that there are nucleated cells in a muscular fibre, and that many of these are applied to the surfaces of its constituent bundles. Of the relation that these cells have to the formation of the muscle substance, if any, we have no knowledge. New methods have shown what the nuclei of muscle really are, and Schultze's theory of the formative activity of the cell must collapse, or find a different basis of support.

Gelatinous fibrillated tissue forms, under favourable circumstances, in the homogeneous plasma that is poured out from the bloodvessels in inflammation. Ranvier has shown that when this tissue forms in the embryo it is distinct from the cells which are mingled with it; and, in a series of experiments I have lately made in cicatrices at various stages, I have always been able to distinguish the cells from the fibrillated tissue. The cells undergo gradual and uniform changes whilst this tissue develops, but it by no means follows that the one set of changes is absolutely dependent on the other. The development of this tissue from the albuminous plasma, which is its matrix, is a question which invites further research. Suggestive remarks on the subject will be found in Paget's "Lectures on Surgical Pathology," and in Cornil and Ranvier's "Manuel d'Histologie Pathologique."

The colourless blood-corpuscles (lymph-corpuscles) that are mingled with the plasma undergo several definite changes, and by means of osmic-acid solution these can be followed with a facility that is impossible by other methods known to us. These cells are the same as those described by Paget as granulation cells; and as I have been able to verify all the stages of transformation described by that author, I will quote his words:—

"The nucleus becomes more distinct; then oval (even before the cell does), and at the same time clearer, brighter, like a vesicle tensely filled with pellucid substance. One or two nucleoli now appear distinctly in it, and soon it attenuates itself; but this it does later, or in a less degree, than the cell; for a common appearance is that of elongated cells bellied out at the middle by the nucleus.

"While these changes are ensuing in the nucleus, each cell also is developing its structure; first becoming minutely, yet more distinctly, granular and dotted. . . . . It elongates at one or both ends, and thus are produced a variety of lanceolate, caudate, or spindle-shaped cells, which gradually elongate and attenuate themselves." [1]

The processes of the spindle cells which are thus formed join each other, and form the connected spindle cells, which can afterwards be demonstrated, by the help of special methods, in fully-developed tissue. The gradual elongation of the colourless blood-corpuscles, and subsequent thinning to the dimensions of a delicate cylindrical fibre, I have observed in the reparative stage of keratitis and in cicatrices.

All the lymph cells which undergo transformation do not become spindle cells. In a great number of them the development of a large round or oval nucleus coincides with the disappearance of all granular protoplasm in the cell, and both cell and nucleus become invisible by almost all the methods hitherto employed in histological investigation. The employment of special methods, and especially that of saturated caustic-potash solution, has during the last few years enabled us to isolate them from the adult tissue in complete layers of polygonal and long, narrow, epithelial-looking cells, in which condition they have until quite recently been hidden from observation. The changes which render them invisible coincide with the development of the fibrillary tissue, and it was hence concluded that they lost their individuality and merged in the newly-formed gelatinous substance. Their isolation from the tissue as fully-developed cells shows that this idea was founded on imperfect methods.

They had indeed been previously observed, but so changed that they could not be recognised. In tissues undergoing absorption the cells lose their vitality, and as they disintegrate become once more visible. Entangled masses of the dead cells have then been, as I have already pointed out, observed and designated "giant cells."

Lymph corpuscles develop also into stellate cells, their ramifying and anastomosing branches becoming the strong resistent fibres which, as in the cornea, for example, bind the bundles together.

The same lymph corpuscles develop into epithelium when they pass amongst the layers of previously-existing cells, or become

[1] *Loc. cit.*, 3d edition, p. 142.

fixed on a denuded surface adjacent to epithelial cells. The observations which I have made regarding this process, and the evidence which I have collected in support of this view, I hope to be able to publish shortly. The importance of the subject merits a fuller treatment than I can give it here.

One of the most striking and essential features of the reparative process which follows or accompanies inflammation, is the formation of new bloodvessels. I can here again only sketch dogmatically what I believe to be the general features of this process, and refer the reader for a more technical discussion of the subject to the *Quarterly Journal of Microscopical Science* for April 1876.

When the injury inflicted by the inflammatory process has so far weakened the bond of union between the epithelial cells which form the tubular lining of a capillary bloodvessel, that blood plasma and corpuscles pass out between them into the lymph spaces between the bundles of connective tissue, in some of the points in the capillary wall the stream enlarges the breach until the blood flows unimpeded into the space. This is the first important and essential step in the formation of a new vessel. The direction of the new development is determined by that of the pre-existing spaces of the tissue. The effused blood is driven by the heart's action in the direction of least resistance. But the blood, when it is in contact with tissues other than the vascular wall, and more readily when the tissues are inflamed, undergoes changes by which a coagulable material present in it forms a membranous substance on the surface of the current, which separates it from direct contact with the surfaces of the bundles. On this membranous substance the colourless blood cells adhere and develop into an epithelium. The vessel is then complete and fit for the transmission of an unaltered blood. Whether the new vessel will be permanent depends not on itself or the blood, but on changes in the tissue in which it is formed.

In the inflamed cornea I have in the walls of newly-forming vessels isolated colourless blood cells in all stages, from that of the normal appearance to a fully developed epithelial cell.

After the very first changes, the cell can only be seen with difficulty. It loses its granular appearance, and acquires a similar refractive power to that of the tissues amongst which it is placed, and can only be detected by the application of special methods. From the wall of young vessels I have further isolated cells, in

transition from colourless corpuscles to the cells of unstriped muscle.[1]

In the interfascicular spaces, the enlarged spindle cells, which I have described as one of the inflammatory changes, can be generally seen before the blood-current enters them. The escape of small rounded bodies from these cells produces an appearance of vacuolation. But this vacuolation is not a vital process connected either with the development of the cell or the growth of the vessel. In the wall of the vessel colourless blood cells elongate and form the spindle cells, which can be afterwards found in the developed tissue as minute cellular elements with fine connecting fibres.

The development of spindle cells into epithelium, which has been described in bloodvessels by Golobew, is not proven. I have never observed it, and as I find that the spindle cells persist as spindle cells, and that the epithelium is developed from lymph-corpuscles, I believe that it is unnecessary to conclude that there is any other mode of formation. Similar facts and arguments apply to other forms of connective tissue.

Observers who have shown that in processes of development in different organs, a diminution of size and disappearance of spindle cells coincide with the development of epithelium, have endeavoured to connect the two processes by supposing that the epithelium was produced by a change in the spindle cells. But the proof is incomplete. The transition has never been shown, and if appropriate methods are applied, I believe that it will be always possible to discover the shrunken spindle cell persisting as a spindle cell. With the disappearance of the granular protoplasm, it had ceased to be visible by the ordinary methods of observation.

The development of bloodvessels in inflamed tissue is similar to that which can be followed in fœtal and young tissue; and to make the theory I have explained more easily intelligible, I append a woodcut, which represents the formation of a capillary bloodvessel as observed in the mouse fœtus.

In this figure, between the developed capillaries, a conical space is to be observed, the base being formed by the wall of the upper,

[1] Arnold, quoted by Paget (*l. c.*, p. 273), found in inflammatory exudation on the free surface of the pleura, "muscular fibre-cells derived from the rounded cells of the inflammatory lymph by gradual elongation; and transitional forms, from the simple lymph corpuscle to the spindle-shaped contractile fibre-cell, were traced in the different layers of the false membrane."

and the apex by a fine line, which is continuous with the first appearance of a similar space, which is connected with the wall of the lower capillary. The large upper space is filled with a faintly granular substance above, and encroached on below by a spindle (or fusiform) cell. In this cell, there are three rounded nuclear bodies. The granular substance produced by the action of the osmic acid in the space is continuous with a similar substance within the bloodvessel, but a faint contour, less distinct in the preparation than in the woodcut, still separates the lumen of the bloodvessel from that of the space. The substance—blood plasma—which fills the space escapes from the vessel between the epithelial cells which form its lining membrane, and which by this mode of preparation are invisible. When the epithelial cells have been sufficiently displaced by the pressure of the blood current, the corpuscles will enter the space. Similar distension and entrance of blood will take place in the small space seen on the upper border of the lower capillary, and the channel between the upper and lower capillary will be completed. The organization of the wall of the new vessel will then take place, Meanwhile, as the space distends, the nuclear bodies seen in the large spindle cell escape into the space, and there present an appearance indistinguishable from blood cells. Their disappearance leaves an apparently empty space, a vacuole, in the spindle cell. What becomes of the spindle cell I do not know, as I have not traced it further; but I am disposed to believe that it disintegrates, and is absorbed. Of this, however, I have no direct evidence.

Fig. 32.—Formation of a new capillary which would have connected two vessels already formed. Mouse fœtus. Osmic-acid prep.—Magn. 300 diam.

It will be well to summarize in a few sentences the general drift of the papers, of which this forms the last chapter. My object has been to show, that when a tissue is the seat of the changes which constitute the condition known as inflammation, these changes are divisible into two categories, the destructive and the reparative. The destructive changes consist, as regards the fibrillary tissue, in swelling, softening, chemical change, and disintegration; as regards the cellular elements, in division of the nuclei into small parts, swelling, death, and disintegration of the cell. The destructive change extends towards the bloodvessels, or directly

implicates them; the weakened vessel permits the escape of the fluid and formed elements of the blood, and with the exhaustion or removal of the cause of the primary destruction, the process of repair begins by organization of the plasma and colourless blood cells. From the former, the ground substance (fibrillary tissue, etc.) is formed; from the latter, all the cellular elements, of what form soever. Flat cells, spindle and stellate cells, non-striped muscle cells, epithelial cells, all owe their origin to the lymph (or colourless blood) corpuscles. But the type of cell once established by the development of the original corpuscle, there is afterwards neither retrogression nor metamorphosis. The epithelial cell never again becomes or produces the colourless blood cell, nor the spindle cell develop into an epithelial cell. *Omnis cellula e cellulâ*, but not in the sense of new cells being begotten by the fixed cells of developed tissue. With the development of the free lymph cell of the fluids into a fixed element of the tissue, the power of reproduction is lost. So much, at least, I believe to be proven in regard to inflammation.

The changes which cells undergo in this process have been erroneously associated with the appearance of colourless blood cells in the spaces of the tissue. Between the one class of phenomena and the other no direct relation had ever been proved, and the results of more rigid observation have shown that none exists.

Had space permitted, I should have discussed the probable nature of the causes which, in one instance, direct the development of a lymph-corpuscle towards the form and qualities of a contractile muscle-cell, and in another of an epithelial cell. That I cannot do so is perhaps the less to be regretted, as such a discussion must have been almost entirely theoretical. In regard to epithelium, however, I may state that I have evidence that one cause of development in this form is to be found in an influence exerted by the contact or immediate juxtaposition of previously-formed epithelial cells.

I will add a few words regarding the mode of treatment I have adopted. In expounding views which, on some of the most vital points in medical science, differ from those taught by authorities whose deserved eminence has, in England at least, approached well nigh infallibility, I felt that proof must be advanced in support of every statement I made. Accordingly, in the earlier chapters, I entered into an amount of histological detail, which demanded an unusual degree of indulgent consideration on the part of readers

of a journal devoted to general medicine. But this full treatment was unavoidable, as it was necessary that I should prepare the foundation for the doctrines which I have afterwards sketched. The shorter treatment, which even the space so liberally granted me has rendered necessary, when I came to consider the question of the formation of new tissue in inflammation, has compelled me to express, with almost aphoristic brevity, opinions which, in the present state of science, would require full and exhaustive discussion. I have endeavoured to supplement this omission by reference to papers which are published elsewhere. Others which are now in preparation, and which are intended to fill the gaps which have been unavoidably left, will probably be published during the year as opportunity offers. In one of these, I shall, as I have already indicated, discuss at length the important question of the regeneration of epithelium. The opinion I have formed regarding its origin was held by Addison, and has been expressed since in Germany by several writers; but the criticism with which it was met by German histologists generally was short and decisive: *sehr gewagt, abenteuerlich,* are epithets applied to it by two writers, whose names have for the moment escaped me. The infancy of a science is the stage in which strong epithets are most plentiful; and judged by this standard, as by many others, histology is still in a position in which difference of opinion is permissible on any point. Holding this opinion, it has not been so much my intention to formulate in these papers a doctrine, as to indicate the results which I believe are to be obtained by the adoption of certain methods. If I have succeeded in arousing the attention of any of our younger histologists sufficiently to induce them to apply these methods for themselves, I feel sure that, whether they see reason to confirm all that I have written or not, they will not fail to contribute something towards our knowledge of the tissues in health and in disease.

I have still in my possession preparations illustrating many of the points which I have discussed, and it will give me pleasure to demonstrate them to any one interested in the subject.

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